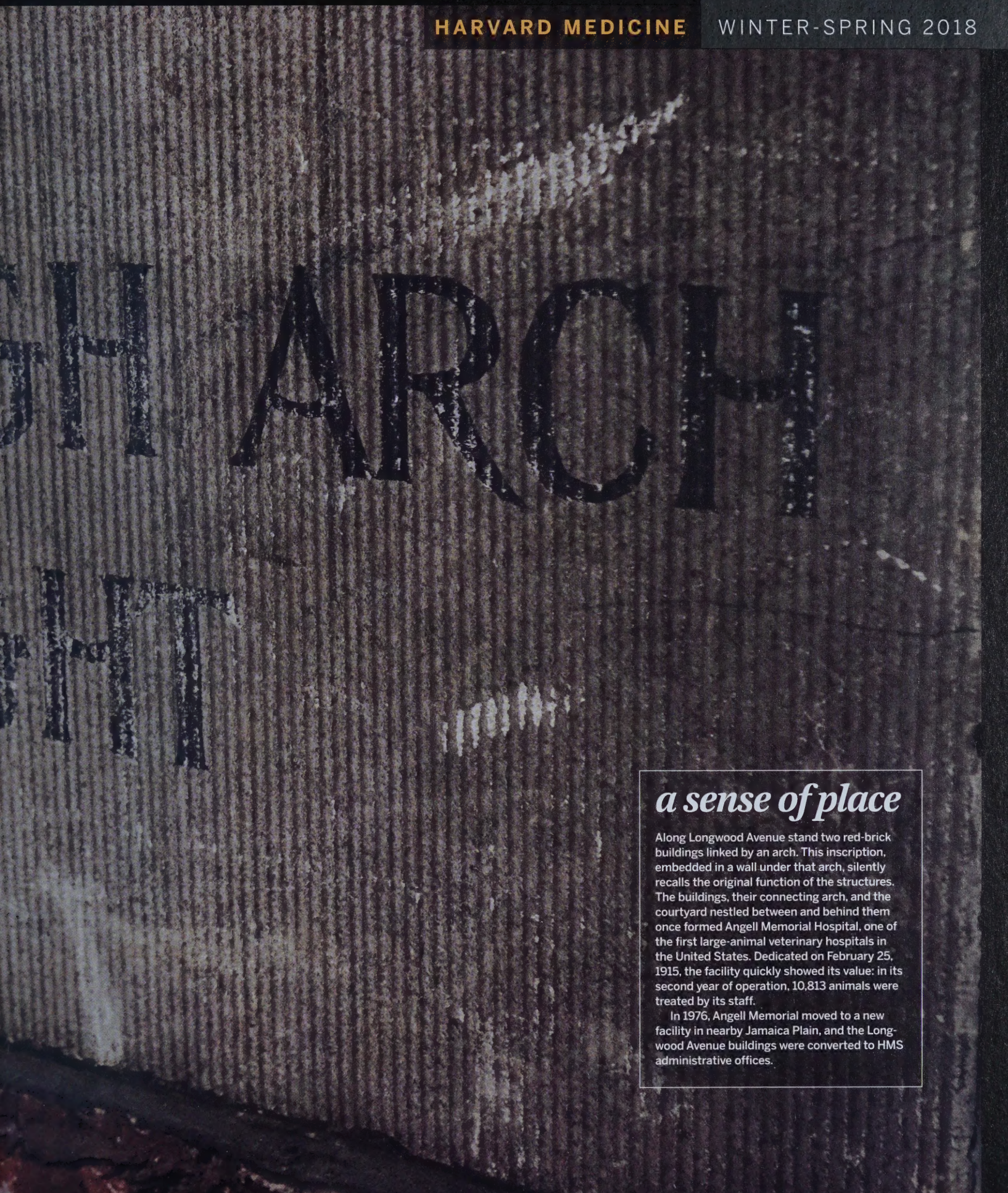


HARVARD medicine

WINTER-SPRING 2018

The Cost of Conflict


HORSES THROU
TO THE



a sense of place

Along Longwood Avenue stand two red-brick buildings linked by an arch. This inscription, embedded in a wall under that arch, silently recalls the original function of the structures. The buildings, their connecting arch, and the courtyard nestled between and behind them once formed Angell Memorial Hospital, one of the first large-animal veterinary hospitals in the United States. Dedicated on February 25, 1915, the facility quickly showed its value: in its second year of operation, 10,813 animals were treated by its staff.

In 1976, Angell Memorial moved to a new facility in nearby Jamaica Plain, and the Longwood Avenue buildings were converted to HMS administrative offices.



p. 11

MARKED AND ALTERED: Members of the U.S. military in Afghanistan suffer injuries that challenge physicians to develop new ways to heal the injured and restore their well-being.

COVER: MATTIAS PAULI



CHRISTOPHE_CERISIER/SIGNATURE/GETTY

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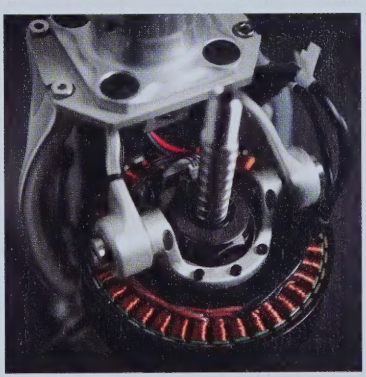
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Crucible of Conflict



IT'S A PARADOX: IN SETTINGS WHERE LIVES ARE SHATTERED, medicine improves.

Many have addressed this incongruity. Atul Gawande, MD '94, for instance, wrote about it in an article penned more than a decade ago for the *New England Journal of Medicine*. Compared with this nation's earlier conflicts, he noted, mortality rates for military personnel in Iraq and Afghanistan had decreased dramatically. In Vietnam, for example, 24 percent of those who sustained injuries died. By contrast, in Iraq and Afghanistan, only one in every ten military personnel who was injured perished. Mortality rates have improved over the years; a 2018 *Journal of Defence and Peace Economics* analysis finds that survival rates in Afghanistan are now nearly 92 percent.

HMS alumni who have served this country have been among those who, when faced with the traumas inflicted by combat, innovated and improved techniques in order to save lives. Those improvements were then used to advance patient care—and were passed along to new generations of physicians.

This dedication to medicine and country continues on our campus.

This dedication to serving medicine and country continues on our campus. Students like Joshua Caldwell, MD 2019, Jonathon Florance, MD 2020, Gregory Galeazzi, MD 2021, Zachary Johannesson, MD 2021, and Zheala Qayyum, MMSc 2019, are veterans of either Iraq or Afghanistan. Others, like Bridget Matsas, MD 2021, a graduate of West Point studying medicine on a military scholarship, intend to dedicate several years to military service after graduating from HMS. Many also carve out time to serve in the National Guard.

Recently, Florance, Johannesson, and Matsas helped found the Civilian-Military Collaborative at HMS, a student interest group that aims to make HMS a leader for civilian-military translational expertise in areas such as trauma care and humanitarian and disaster response. The students say the collaboration, like medicine and the military, allows them to work as a team, united in their commitment to selfless service.

Like so many of the HMS student initiatives I've had the privilege of witnessing, this collaborative is tied to a national movement, one that would integrate military and civilian trauma systems. This effort, enunciated in a 2016 report from the National Academies of Sciences, Engineering, and Medicine, aims to achieve "zero preventable deaths after injury" by ensuring that "lessons learned from the military's experiences in Afghanistan and Iraq are sustained and built on for future combat operations—and that they are translated into the civilian system." HMS leadership is in evidence in this initiative, too: The recommendations were crafted by a group led by Donald Berwick, MD '72, and including Cato Laurencin, MD '84.

At HMS, we pride ourselves on building leaders in medicine. But we also take pride in watching those leaders shape our profession, our nation, and our world.

George Q. Daley
Dean of Harvard Medical School

HARVARD medicine

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RANDY GLASS

"I was surprised to see myself in the photo of students eating in the Vanderbilt dining hall."

A Kodak Moment

IN THE AUTUMN 2017 ISSUE of *Harvard Medicine,* I was surprised to see myself in the photo (p. 51) of students eating in the Vanderbilt dining hall. I'm at the table in the foreground of the picture where seven Black students are seated. I am the one who is facing forward and smiling directly into the camera. I'd like to know if I could get a digital image of this photo.

I lived in Vanderbilt Hall in 1972 until, maybe, 1974. I graduated in 1976 and recently returned for my fortieth class reunion. Lots of memories from that time. I wish I had gotten to know more of my classmates better during my stay in Boston.

WESLEY CURRY, MD '76
EMERYVILLE, CALIFORNIA

Ed.: We shared the information Dr. Curry provided with the archivist in the Center for the History of Medicine at the Countway Library. We also sent Dr. Curry a digital copy of the photo—along with our thanks for his sharing a bit of HMS history with us.

A Westerly Breeze

I THINK THE AUTUMN 2017 ISSUE of *Harvard Medicine* is beautifully done, but I do have a question about the photo (pp. 12-13) that opens the story "Inherit the Wind." The accompanying text, which refers prominently to the New England dust cloud in 1934, leads the reader to assume that the photo relates to that event. Judging by the cars, signs, and buildings in the image, however, it would appear to be a much more recent scene from Boston or elsewhere. Perhaps I'm mistaken, but if not, some attribution would be welcome. I don't recall anything like this in Boston during my fifty-odd years here.

Keep up the great work you're doing with the magazine.

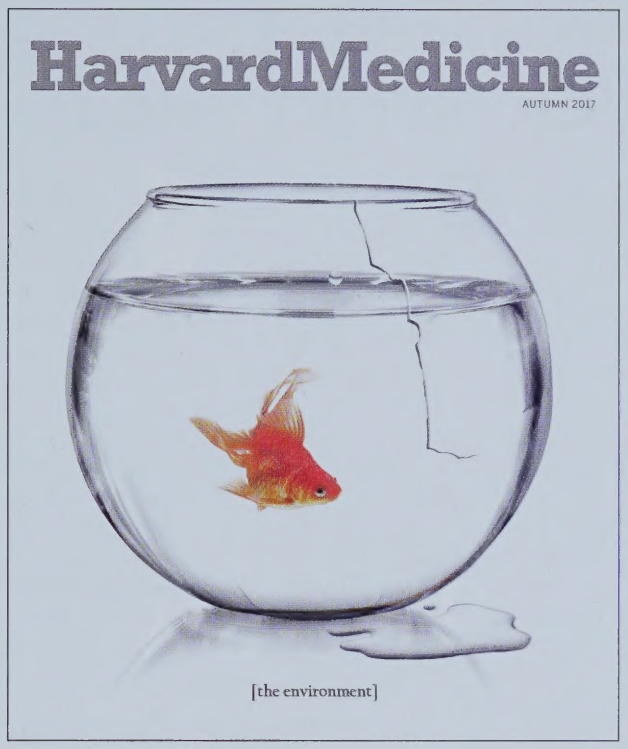
PAUL CHAPMAN, MD '64
BOSTON, MASSACHUSETTS

Ed.: Dr. Chapman is correct; the image is of a 2013 dust storm in Phoenix, Arizona. Although we included this information in the online version of the story, his keen eye and thoughtful letter allow us to clarify the photo's time and place for readers of the print version.

Foresight and Oversight

ONE CAN IMAGINE MY SURPRISE when I picked up *Harvard Medicine*'s issue on the environment (Autumn 2017) and found no mention of the Center for Health and the Global Environment, which I founded at HMS in 1996 and directed for more than sixteen years. The first such institution at a U.S. medical school, the center focused on the health consequences of climate change, loss of biological diversity, ozone depletion, and other aspects of global environmental change.

Paul Epstein, Daniel Goodenough, Howard Hu, and I, later joined by others, taught a highly popular course, offered by HMS and then by the Harvard T.H. Chan School of Public Health, on these subjects for ten years, drawing students from throughout the University, and distributed it online and as videotaped lectures to sixty-five medical schools and universities in many countries. For a decade, we also taught a similar course for U.S. congressional staffers and organized twenty-three congressional briefings on a range of environmental health issues. Speaking around the world and publishing widely, we were



a major educational resource, well ahead of others, for our medical and scientific colleagues, representatives in Congress and the United Nations, the media, and the public. We translated the abstract, technical, complex science of global environmental change into the concrete, personal, everyday language of human health.

The center, now based at the Harvard Chan School, is directed by Gina McCarthy, a professor of public health practice at the school who was the administrator of the U.S. Environmental Protection Agency under President Barack Obama. More than two decades after its founding at HMS, the center continues to do groundbreaking work, now more important than ever.

ERIC CHIVIAN, MD '68
BOSTON, MASSACHUSETTS



Too sweet

PHYSICIANS OFTEN ADVISE PEOPLE who suffer from fatty liver disease and other metabolic diseases to cut calories, especially those from concentrated sugars such as high-fructose corn syrup. Research conducted by HMS scientists has shown how good that advice may be. The tests, conducted in mice, placed the animals on regular or high-fat diets that included plain water or water sweetened with fructose or glucose, a component of table sugar. Animals fed a high fat/high fructose diet became more obese and more insulin-resistant than their high-fat/high glucose-eating peers. The researchers also found that levels of a protein required for fructose metabolism, but not for glucose breakdown, increased in the livers of mice that drank fructose.

Softic S, et al., *Journal of Clinical Investigation*, November 2017

MATTIAS PALUDI

VIRAL REGULATION

Protein acts as alarm clock for herpes infections

ONCE HERPES SIMPLEX INFECTS A PERSON, the virus takes up permanent residence inside nerve cells, periodically reigniting infection and causing cold sores or genital lesions to recur.

How the virus maintains this sleep-wake mode has been unknown. Now, HMS scientists in the Department of Microbiology and Immunobiology and the Department of Biological Chemistry and Molecular Pharmacology have used a mouse model to identify the molecular regulator of this viral lifestyle: a host cell protein called CTCF, or cellular CCCTC-binding factor.

The researchers found that CTCF enables herpes simplex to establish latent infections in the body's sensory neurons. Preventing CTCF from binding to the viral DNA weakens the virus's ability to rekindle infection and its associated symptoms.

Previous research at HMS showed that the virus's sleep-wake cycle is regulated by the interaction of two sets of genes. Latency-associated transcript genes, or *LAT* genes, turn off the transcription of viral RNA, which induces viral latency, while a gene called *ICP0* produces a protein that activates genes that stimulate viral replication, leading to active infection. Past studies have shown that the *LAT* gene and the *ICP0* gene can act in opposition, inducing the virus to alternate between dormant and active states, but can also act in concert to promote latency or reactivation. The genes also occupy overlapping sites on the viral genome.

In a series of experiments, the recent study identified the sites on the virus's DNA where the CTCF protein binds and showed that deleting the CTCF binding sites weakened the virus's ability to awaken from its dormant state, strong evidence that the CTCF protein is a key regulator of the sleep-wake cycle in herpes simplex infections.

Lee JS, et al., *mBio*, January/February 2018

Genetics

Species offers a chance to learn how animals survive traits that sicken humans



Cavefish experience blood-sugar spikes and crashes after eating, yet they remain healthy. Scientists hope that studying the cavefish's genome will reveal genes that protect against blood-sugar dysregulation, knowledge that could help humans, too.

Riddle MR, Aspiras AC, et al., *Nature*, March 2018

IMMUNE RESPONSE

Lung infections can turn fatal if nerve cells intervene

WHEN THE BODY IS FIGHTING infection, the immune system kicks into high gear. It may not be acting alone, however. Research by HMS scientists indicates that the nervous system may also be involved, particularly in deadly lung infections.

In work carried out in mice, scientists in the HMS departments of Microbiology and Immunobiology and Cell Biology, the Evergrande Center for Immunologic Diseases at HMS, Brigham and Women's Hospital, and the University of Calgary in Alberta, Canada, found that neurons carrying nerve signals to and from the lungs suppress immune response during infection with *Staphylococcus aureus*. This bacterium, which is growing increasingly impervious to antibiotics, has emerged as a top killer of hospitalized patients.

In the lungs, sensory neurons detect mechanical pressure, inflammation, temperature change, and the presence of chemical irritants, then send an alert to the brain—a notification that can come in the form of pain, airway constriction, or a cough that expels harmful agents or particles from the airways.

This study, however, revealed that when mouse lungs are invaded by staph bacteria, sensory neurons reduce the lungs' ability to summon several types of disease-fighting cells in response to infection. A second set of experiments showed that disabling these neurons in mice promoted immune-cell recruitment, increased the lungs' ability to clear bacteria, and boosted survival in staph-infected mice.

According to the researchers, the results suggest that different classes of sensory neurons may be involved in restraining or promoting immune response. These findings could pave the way to nonantibiotic therapies for bacterial pneumonia that would target neuroimmune signaling in the lungs.

Baral P, et al., *Nature Medicine*, March 2018

AGING

Time's toll reversed by bolstering blood vessels

AS WE AGE, our tiniest blood vessels wither and die, depriving muscles of oxygen and allowing wastes to build up and affect muscle health. Scientists have long wondered whether reversing the aging of blood vessels could help us maintain our youthful vigor. In work by researchers in the Department of Genetics at HMS, the answer appears to be yes, at least in mice. The achievement, the research team said, paves the way to identifying related therapies for humans.

The study focused on endothelial cells, which line blood vessels and are essential for the health and growth of blood vessels that supply oxygen-rich and nutrient-loaded blood to tissues. As endothelial cells age, blood vessels atrophy, new blood vessels fail to form, blood flow to muscles lessens »

» and muscles weaken. Although this weakening process can be slowed with regular exercise, over time, the effects of such beneficial efforts become less effective.

In a series of experiments, the scientists found that reduced blood flow develops as endothelial cells start to lose a critical protein known as sirtuin1, or SIRT1. They also found that SIRT1 loss is precipitated by the loss of NAD+, a key regulator of protein interactions and DNA repair. Previous studies have shown that SIRT1 delays aging and extends life in yeast and mice and that NAD+, which also declines with age, boosts the activity of SIRT1.

The experiments showed that in young mouse muscle, SIRT1 signaling is activated and generates the tiny new blood vessels that supply oxygen and nutrients to tissues. As NAD+/SIRT1 activity decreases over time, however, so does blood flow, leaving muscle tissue nutrient deprived and oxygen starved.

The study also showed that SIRT1 may be the molecule that relays growth-factor signaling from muscles to blood vessels, a signaling chain that induces blood vessel formation. It further showed that endothelial cells lacking SIRT1 fail to recognize signals from growth factors released by exercised muscles, explaining why age-related loss of SIRT1 leads to muscle atrophy and blood vessel death.

To test whether boosting SIRT1 levels would affect these declines, the scientists used NMN, a NAD+ precursor known to play a role in repairing cellular DNA and maintaining cell vitality. When NMN was given over two months to a group of 20-month-old mice, an age equivalent to about 70 years in humans, NMN restored the number and density of blood capillaries to that seen in younger mice. Blood flow to the muscles also increased and was significantly greater than blood supply to the muscles seen in same-age mice that didn't receive NMN.

Das A, et al., *Cell*, March 2018

SIRT1 may relay growth-factor signaling from muscles to blood vessels, inducing vessel formation.



ANTIBODIES

In the search for new drugs, yeast rise to the occasion

RESEARCHERS HAVE FOUND a new way to create valuable antibodies without needing llamas. Yes, llamas.

Llamas, alpacas, camels and other members of the camelid family produce a class of antibodies that allow scientists to determine the structures of otherwise impossible-to-study proteins in the body, understand how those proteins malfunction in disease, and design new drugs that act on them.

Use of camelid antibodies, however, is not without its downsides.

First, not all investigators who need such antibodies have access to llama (or alpaca or camel) facilities. Second, while the animals aren't harmed, vaccinating them to generate the desired antibodies is expensive, takes as long as six months per attempt, and often doesn't work.

A team of structural biologists from the HMS Department of Biological Chemistry and Molecular Pharmacology and from the University of California, San Francisco, have now created a llama-free solution: vials of specially engineered yeast.

The yeast method can be done in a test tube in a researcher's own lab and has a higher success rate and faster turnaround time than both llama vaccination and previous attempts to circumvent use of camelids. The yeast system has been made freely available for nonprofit use.

The active segments of camelid antibodies are often called nanobodies because they can be much smaller than regular antibodies. A llama nanobody might bind only to a particular conformation—for example, "open" or "closed"—of a particular protein. Nanobodies can also bind to challenging proteins, such as receptors that work in oily cell membranes.

Structural biologists want to find the exact nanobody that matches their protein of interest so they can lock the protein in one position and run tests to figure out its atomic structure. According to the researchers, nanobodies could make it possible to develop drugs for biological targets that antibodies are simply too big to hit.

The HMS research team has already created a library of 500 million camelid antibodies using yeast cells. Each yeast cell has a slightly different nanobody tethered to its surface, made by a slightly different piece of synthetic DNA.

McMahon C, et al., *Nature Structural & Molecular Biology*, March 2018

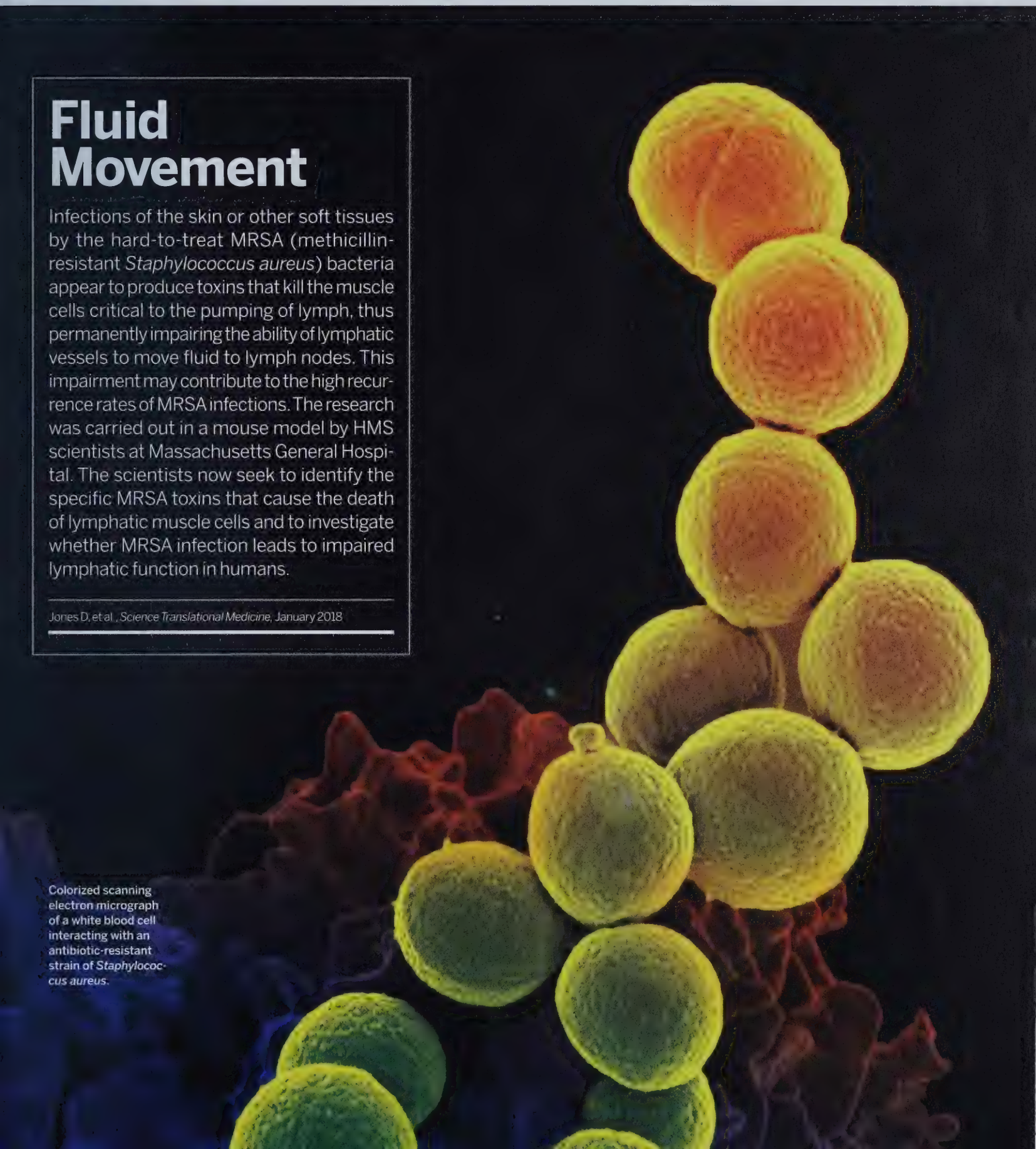
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HM INDEX: STAPHYLOCOCCUS AUREUS *IS FOUND ON THE SKIN AND IN THE NOSE OF* **3** *IN EVERY* **10** *PEOPLE; MRSA IS CARRIED BY* **2** *IN* **100**.

Fluid Movement

Infections of the skin or other soft tissues by the hard-to-treat MRSA (methicillin-resistant *Staphylococcus aureus*) bacteria appear to produce toxins that kill the muscle cells critical to the pumping of lymph, thus permanently impairing the ability of lymphatic vessels to move fluid to lymph nodes. This impairment may contribute to the high recurrence rates of MRSA infections. The research was carried out in a mouse model by HMS scientists at Massachusetts General Hospital. The scientists now seek to identify the specific MRSA toxins that cause the death of lymphatic muscle cells and to investigate whether MRSA infection leads to impaired lymphatic function in humans.

Jones D, et al., *Science Translational Medicine*, January 2018



Colorized scanning electron micrograph of a white blood cell interacting with an antibiotic-resistant strain of *Staphylococcus aureus*.

noteworthy

LGBTQ elective innovates by including clinical experience

THE SCHOOL RECENTLY INTRODUCED a new LGBTQ health clinical elective course for medical students. The elective is a month-long multidisciplinary clinical and scholarly experience that trains students to provide high-quality care to patients who are LGBTQ, gender nonconforming, or born with differences of sex development. The course focuses on having the students work with youth but also provides clinical exposure to and education on working with LGBTQ adults. Clinical settings include psychiatry, adolescent and young adult medicine, pediatrics, family practice, and internal medicine.

According to Robert Kitts, an HMS assistant professor of psychiatry at Massachusetts General Hospital and a former course co-director, the LGBTQ course at HMS places an emphasis on clinical experience, unlike the primarily classroom-based courses at most U.S. medical schools. Kitts notes that the course was created in response to a growing demand from faculty and students for such a clinical elective.

Neir Eshel, MD '13, PhD '14, a resident at Stanford University Medical Center, says that he and a few other students began lobbying for broader institutional support for LGBTQ students shortly after their arrival at HMS.

The course has received welcome support from prominent alumnus Neal Baer, MD '96 (*fig. 1*), who has given HMS $250,000 to establish an endowed scholarship to support MD students interested in LGBTQ health. Baer, an award-winning writer and producer for the television shows *China Beach* and *ER*, is an adjunct professor of preventive medicine at UCLA's Fielding School of Public Health.

Infusion of new support aims to spark therapeutics research

A RECENT SURVEY designed to measure faculty interest in translating basic research into novel treatments elicited responses from nearly 900 HMS faculty, a pool that included professors in the School's basic science departments and principal investigators in Harvard-affiliated hospitals.

The results showed that although most respondents characterized their work as basic science research—83 percent of Quad-based researchers and 64 percent of hospital-based investigators—88 percent of all respondents said their work has identified pathways and targets that could be used to develop therapeutics. Of those respondents, nearly three-fourths said they had themselves initiated efforts to develop drugs, primarily by screening the therapeutic potential of small molecules.

A lack of funding was the obstacle most often cited as limiting more vigorous pursuit of therapeutics research. (*fig. 2*)

The School is readying an initiative to help overcome that hurdle and help satisfy the faculty's hunger to advance fundamental research toward therapeutics. For the past few months, a task force led by Nathanael Gray, the Nancy Lurie Marks Professor of Biological Chemistry and Molecular Pharmacology in the Field of Medical Oncology, and Timothy Mitchison, the Hasib Sabbagh Professor of Systems Biology, has explored how HMS might become better at translating fundamental scientific insights into therapeutics.

The task force's several recommendations include new programs and platforms that can be used by all HMS faculty to identify therapeutic targets and strategies; formulate small molecules, proteins, antibodies, genes, and cells; and move potential therapies through clinical proof of concept and regulatory approval. In addition, the School has already launched a therapeutics track in its PhD program and, in what will be an ongoing effort to build collaborations with leaders in academia, business, industry, and politics, plans to host annual innovation summits.



fig. 1

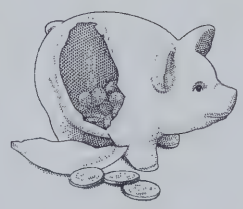


fig. 2



fig. 3

Redesigned curriculum gets students engaged and in class

ASSESSMENTS OF THE EFFECTIVENESS of the Pathways curriculum are accumulating, and the data are more than encouraging.

In 2015, HMS launched Pathways, a major redesign of the School's medical education curriculum. In the new curriculum, students experience fourteen months of intensive scientific training followed by a year of full-time clinical immersion. Informed by the insights gained during this time in clinic, the students then return to the classroom to immerse themselves in biomedical research.

One of the design goals of the new case-based collaborative learning pedagogy in the Pathways curriculum is to increase the level of student engagement; data from the American Association of Medical Colleges Year 2 Student Questionnaire already shows progress toward that goal. The national benchmark data in the AAMC survey shows that only about 50 percent of medical students actually attend class during the basic science, preclerkship phase of the curriculum. HMS was about at that national average in the years before the rollout of Pathways, but data from the new curriculum's first cohorts show that this percentage has jumped to 97 percent participation in class—a significant increase.

This same success is now being seen with the new advanced integrated science courses (AISCs) that members of the leading-edge class in the Pathways curriculum are taking during their post-clerkship phase. The eight AISCs aim to provide medical students with the skills they need to evaluate new research advances and incorporate them into their clinical decision making as physicians. The curriculum requires every medical student to take two of these courses.

"The AISCs are getting the best student reviews we've ever seen," says Edward Hundert, MD '84 (*fig. 3*), HMS dean for medical education, "and we're seeing evidence of an incredible level of engagement."

The Cost of Conflict

With each day, the conflict in Afghanistan becomes an even longer longest war in U.S. history. But, it has not been our deadliest. Although weaponry has become more lethal, and explosive injury more common, improvements in medical care and treatment have kept the wounded alive. The injuries sustained, however, are severe and life-altering.





Here, Yet Not Here

When traumatic events etch themselves in the brain, behavior, well-being, and even the perception of reality can become altered, disrupting daily life

BY KEVIN JIANG

Throughout most of his life, John Bradley has, in one form or another, lived with post-traumatic stress disorder. As a youth, he witnessed his father, a career officer and two-tour veteran of the Vietnam War, struggle with it. And, as a physician who served multiple deployments, including a tour in Iraq, Bradley experienced it himself.

"For months after returning from Iraq, I would hear small-arms fire as I fell asleep each night," says Bradley, an HMS associate professor of psychiatry and a retired U.S. Army colonel. "I experienced hyperarousal symptoms and anxiety. I've absolutely been affected by PTSD."

Bradley credits his psychiatry training for helping him recognize his symptoms and manage them effectively using the same approaches he uses for his patients. But he was also aided by the example of his father.

"I chose psychiatry as a specialty and the military as a career because of my family. I saw the profound effect that combat experience had on my dad and the burden that he carried and continues to carry with him," Bradley says. "Nevertheless, his life has had a great deal of effectiveness and joy."

Despite never receiving treatment for PTSD and exhibiting symptoms even into his eighties, Bradley says his father lived a full, healthy life by being able to reconcile his combat experiences with his civilian life. This personal observation has been important for Bradley, who, in his role as chief of psychiatry and deputy director for the mental health service at the VA Boston Healthcare System, oversees psychiatric practice and professional development for hundreds of mental health clinicians and staff.

"The question I think we should be trying to help those with PTSD answer is: 'Can you regain effectiveness in your life, whether that's with your family or with your job, even when the symptoms occur?'" Bradley says. "Yes, you want to control symptoms so that people can function, but the more important therapeutic issue is really an existential one: 'Can you develop a narrative you can live with?'"

Researchers at HMS and elsewhere are working to develop an understanding of PTSD's many facets in the hope of improving diagnosis of the disorder and developing treatments that can help and heal. But the task is daunting: The disorder is rooted in biology and medicine, weighted with cultural constructs that shape self-perception and expectation, and, according to a growing number of experts, deepened by one's personal moral code.

The War at Home

Since 2001, nearly three million U.S. servicemembers have been deployed to Afghanistan and Iraq. During their time overseas, most of these soldiers witness or live through life-threatening traumatic events. When they return home, as many as 20 percent develop PTSD.

The symptoms of PTSD can be disabling: persistent nightmares, flashbacks, avoidance of reminders of a traumatic event—including one's own thoughts and feelings—negative worldview, and increased physiological tension or hyperarousal. PTSD trails only tinnitus and hearing loss as the most common disability for which veterans receive compensation from the VA. In more than half of the people diagnosed with the disorder, PTSD co-occurs with depression, substance abuse, traumatic brain injury, or other psychological and physiological manifestations. This constellation of burdens can turn the activities of daily life into insurmountable obstacles.

The social and economic costs are enormous. According to a 2008 RAND Corporation analysis, "PTSD and depression among returning service members will cost the nation as much as $6.2 billion in the two years following deployment—an amount that includes both direct medical care and costs for lost productivity and suicide."

In 2013 documents, the VA reported treating more than a half million veterans with primary or secondary diagnoses of PTSD. These veterans are more likely to have marital, relationship, and parenting problems and to be at increased risk for violence and suicidal thoughts. Between 2004 and 2009, 60 percent of the $3.7 billion spent by the VA on veterans' health care was related to PTSD treatment.

Age-Old Suffering

For as long as humans have experienced war, conflict, and trauma, they have suffered from PTSD. It's just often been called something else.

In the *Epic of Gilgamesh*, a work of literature dating back some 4,000 years, a Sumerian king, Gilgamesh, suffered nightmares and wandered numb through his kingdom after witnessing the death of his friend Enkidu. Another ancient example can be found in the *Ramayana*, an epic Indian poem from the fifth millennium BCE. The poem details the terror-filled recollections of the demon Marrich after he was almost killed by the hero Rama—Marrich goes so far as to avoid the mention of things that start with the letter *R*.

In the 1600s, doctors in Europe noted that Swiss mercenaries were increasingly gripped by despair, sleeplessness, and severe homesickness, a condition they dubbed nostalgia. During the U.S. Civil War, physicians found that nostalgia was often accompanied by mania, withdrawal, or destructive behaviors. Veterans exhibiting these symptoms filled post-war asylums.

During World War I, soldiers afflicted with nightmares, tremors, and psychological and physical disorientation were said to be suffering from shell shock, while World War II saw this array of symptoms come to be known as battle fatigue or combat stress reaction. The symptoms were chalked up to exhaustion from long deployments.

John Bradley



A new discourse about such symptoms, however, started percolating during the Vietnam War. Sparked by the 1972 *New York Times* op-ed column, "Post-Vietnam Syndrome," by Canadian psychiatrist Chaim Shatan, the medical community began to investigate in earnest the psychological consequences of combat stress.

By the Book

Psychiatrists formally acknowledged PTSD as a medical disorder in 1980, including criteria for its diagnosis in the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*.

The primary diagnostic criterion was based on whether an individual had been exposed to an overwhelming stressor, one on the edges of normal human experience, such as war, sexual assault, and catastrophic disasters, natural or otherwise. This perspective was a dramatic shift in thinking; the disorder went from being a condition resulting from personal weakness to one initiated by external forces that swamped a person's ability to cope.

The National Comorbidity Survey Replication, conducted between February 2001 and April 2003, estimated that nearly 7 percent of adults in this country would, at some point in their lifetime, develop PTSD as a result of exposure to traumatizing situations such as domestic abuse and serious accident or injury. Yet the nature of war—the repeated, unavoidable exposures to death, horror, and trauma—binds the disorder to the experience of soldiers. Addressing the causes of and treatment for PTSD, therefore, is a central part of the mission of the Veterans Health Administration, the federal health care system responsible for the medical needs of an estimated



Daily encounters with the ruins of lives and communities can become troubled memories that remain with veterans for decades.

20 million veterans, many of whom struggle with PTSD for much of their lives.

"I still encounter World War II veterans who, as you engage them in conversation during a visit, will start to cry and talk about things that happened more than seventy years ago," says Michael Charness, an HMS professor of neurology and chief of staff of the VA Boston Healthcare System.

A Window Within

According to Charness, there has been a growing acceptance that PTSD is a bona fide disorder that affects the structure and function of the brain. Some of the earliest and strongest evidence for its biological basis arose from studies conducted by VA scientists in the late 1980s, including those led by Roger Pitman, now an HMS professor of psychiatry and director of the PTSD research laboratory at Massachusetts General Hospital, and his colleagues.

Adapting an experimental paradigm known as script-driven imagery, Pitman and colleagues asked combat veterans to describe their traumatic experiences and detail how they felt during those experiences. The researchers then composed short personalized scripts based on the descriptions and measured participants' biological responses as the scripts were read aloud back to them. Participants were instructed to remember the moment as vividly as possible.

In one set of experiments, published in the *Archives of General Psychiatry* in 1996, Pitman's team used this approach while scanning the brains of PTSD patients. Those scans found that the brain regions involved in responding to threats—those areas involved in the fight or flight response—were hyperactive, particularly the amygdala, which plays a primary role in emotion and fear, and the dorsal anterior cingulate cortex, which connects the amygdala with a cortical region responsible for inhibiting cognition and executive function. At the same time, the region of the brain that plays a role in inhibiting emotional responses appeared to be underactive.

In other studies, says Lauren Lebois, an HMS instructor in psychiatry in the Neurobiology of Fear Laboratory at McLean Hospital, brain scans of people diagnosed with PTSD have shown the opposite response.

"What we've seen from functional neuroimaging studies is that brain activity in individuals with PTSD can go awry in two different directions," says Lebois. "In some individuals, the parts of their brains responsible for the stress response become overactive and the parts that act as

"I still encounter World War II veterans who, as you engage them in conversation, will start to cry and talk about things that happened more than seventy years ago."

braking mechanisms to the stress response are underactive compared to individuals without PTSD. In a subset of other individuals with PTSD, threatening stimuli trigger the opposite sort of brain pattern—parts of their brains responsible for stress response become underactive and parts that act as braking mechanisms to stress response become overactive."

As technologies advance so do efforts by researchers to identify the molecular and genetic factors associated with PTSD. As with other psychiatric disorders, PTSD likely involves the interaction of various genes that contribute to its development and progression, a fact that underscores the need for initiatives such as the VA's Million Veteran Program. As of September 2017, this program had collected blood and DNA samples as well as electronic medical records and longitudinal health and lifestyle surveys from more than 600,000 veterans, making it the world's largest genomic database tied to a health care system.

With the goal of collecting all one million samples by 2020, program researchers aim to provide scientists with the data and statistical power needed to better understand, diagnose, and treat complex diseases. Studies on PTSD and substance abuse are already underway.

Soul-Wrenching

War breeds experiences that, under normal circumstances, would be unthinkable for most people: harming or killing civilians; following illegal or immoral orders; witnessing atrocities committed on noncombatants or fellow soldiers; failing to intervene or report such acts. Any of these experiences can challenge a soldier's core moral and ethical beliefs.

Moral injury is a framework for understanding what happens when war transgresses deeply held ethical beliefs.

Bradley still relives one such moment. He was commanding a four-vehicle convoy moving through the streets of Najaf, Iraq, when the Humvees crossed paths with a procession celebrating the festival of Eid al-Fitr, the end of the month of Ramadan. The soldiers' presence at the holy celebration infuriated the crowd. Soon, the Humvees were being rocked in an attempt to flip them. Bradley and his team freed themselves the only way they could.

"We drove back and forth to push the assailants away," says Bradley. "We were able to extricate ourselves, but we wounded a number in the crowd."

According to Alex Jordan, a staff psychologist at McLean Hospital who has served as the PTSD expert evaluator for the VA and Department of Defense jointly funded Consortium to Alleviate PTSD, military servicemembers "are trained to deal with threats to their life but not as much for dealing with the other realities of combat."

"Many are haunted most by events that didn't cause them to feel terror, but rather shame, guilt, anger, or resentment," he adds. "This violation of moral expectations that one holds for oneself or other people may cause what we call moral injury." Jordan has co-authored several publications on moral injury, including, in 2017, a clinical primer on the spiritual features of war-related moral injury in the journal *Spirituality in Clinical Practice*.

Coined in the late 1990s by VA Boston psychiatrist Jonathan Shay, moral injury is a still-developing framework for understanding what happens to humans when their deeply held ethical and moral beliefs are transgressed in war. Unlike with PTSD, which is diagnostically tied to a traumatic event, the criteria for determining moral injury are still unclear: A person's perception of traumatizing events must be reconciled within broader social, spiritual, cultural, and moral contexts. The consequences for those affected include emotional numbing, avoidance, withdrawal, and depression, echoes of the symptoms those diagnosed with PTSD experience.

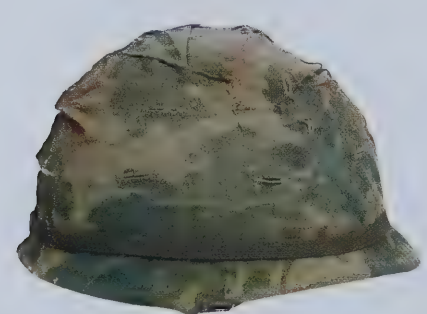
"It was clear to me many years ago that our paradigm for PTSD was not sufficient," says Brett Litz, a professor in the Department of Psychiatry at the Boston University School of Medicine and a psychologist at the VA Boston Healthcare System, who has spent the better part of the past two decades studying unusual aspects of military-related psychic damage.

"There is an expectation that all traumas are alike in the diagnostic manual," he adds, "but war trauma has a completely different sociocultural context from most others." In 2009, Litz authored a review that presented a preliminary model and intervention strategy for moral injury. He has since published several studies on the topic, including one describing the first potential treatment specifically for moral injury, an exposure-based intervention called adaptive disclosure.

"The stakes are higher for war. The loss of life, the grotesque nature of armed conflict, these affect the humanity of people who feel they're engaging in something honorable," Litz adds. "This incongruity can leave a lasting harmful effect."

The Core of the Matter

In an effort to develop insights for possible new treatments for PTSD, Milissa Kaufman, an HMS instructor in psychiatry, and, at McLean Hospital, medical director of the Hill Center for Women and director of the Dissociative Disorders and Trauma Research Program, has been using imaging and genetic and neurocognitive testing



The National Vietnam Veterans Readjustment Study, conducted in the late 1980s, estimated that

15 of every 100

male Vietnam veterans had been diagnosed with PTSD. According to the National Center for PTSD,

11 to 20 of every 100

veterans of Operation Iraqi Freedom and Operation Enduring Freedom receive a diagnosis of PTSD in a given year.

ZIM286/ESSENTIALS/GETTY



Milissa Kaufman (left) and Lauren Lebois

to determine how different conditions contribute to and interact with PTSD. Her studies focus on women who have been diagnosed with PTSD and have multiple co-occurring medical and psychiatric issues.

"PTSD is very complicated, and there are many factors that have to be considered at the same time," says Kaufman. "But PTSD is PTSD. Patients will have intrusive memories, physiological responses to triggers, avoidance behaviors, and negative perspectives on themselves and the world around them. There are well-validated, empirically based treatments that can help them."

Clinical trials have shown that approaches such as cognitive processing therapy, which teaches patients to evaluate and change their thoughts about their trauma, and prolonged exposure therapy, which helps patients overcome avoidance by confronting their memories and feelings, effectively reduce the severity of PTSD symptoms. Reviews of these therapeutic approaches have shown that, depending on the study parameters, one-half to two-thirds of those who complete treatment demonstrate clinically meaningful improvement or no longer meet the diagnostic criteria for PTSD.

While psychotherapy is the clear frontline treatment for PTSD, augmenting that therapy with medications such as antidepressants, which block the reuptake of certain neurotransmitters, have been shown to help modulate mood and anxiety in some cases. Many other pharmaceuticals have been evaluated or are undergoing evaluation for PTSD, including antipsychotics, mood stabilizers, and antianxiety medications. More recently, the use of synthetic dissociative drugs such as ketamine and psychoactive agents such as MDMA have been explored. Evidence of efficacy, however, remains scant for the majority of these drugs.

Ensuring that those affected with PTSD seek and adhere to treatments is not an easy task. Social stigma can cause patients to shun help and dismiss treatment. Recent surveys by the National Academy of Sciences have found that about 50 percent of the veterans who need mental health help, particularly those without close family and friends, do not seek treatment.

In an effort to increase the number of veterans who do seek help, the VA and its partners have launched initiatives that deliver treatments virtually, allowing access through personal computers and handheld devices. Complementary medicine approaches, from yoga and meditation to acupuncture and the use of virtual reality technology, also are being explored. There is some evidence that, when combined with standard treatments, these approaches can have a beneficial effect.

Even as research into the causes, symptoms, epidemiology, and treatment for PTSD continues, the condition that has accompanied human conflict for millennia still shows itself through its effects on individuals, families, and communities. Conflict may always be with us, but the drive to find ways to decipher, prevent, and alleviate the trauma it engenders will always be there as well. HM

Kevin Jiang is a science writer in the HMS Office of Communications and External Relations.

"There is an expectation that all traumas are alike in the diagnostic manual, but war trauma has a completely different sociocultural context from most others."

Melvin Glimcher and the invention of the myoelectric elbow

The Art of Motion

BY STEPHANIE DUTCHEN



A high-speed, stop-action photo of a patient using the "Boston Arm," an electric elbow with myoelectric control.



COURTESY MIT MUSEUM

The first time Melvin Glimcher, MD '50, tried to enlist in the Marines, his mother dragged him out of the recruiting office. He was 17.

His second try succeeded, although not precisely as he had hoped. Instead of being sent to the front lines of World War II, Glimcher was deemed "too smart" for combat and was dispatched to college to study physics and mechanical engineering. A medical degree followed, *magna cum laude*.

As the field of orthopedics came of age, Glimcher became a pioneer in biomechanics, publishing iconoclastic papers on bone formation, bone structure, and gait. He also collaborated on the development of the first bionic elbow.

Dubbed the Boston Arm, this device changed the lives of upper-limb amputees, including military veterans.

In the late 1950s, Glimcher was spending one day each week at the Liberty Mutual Insurance Company in Boston, treating patients who had lost limbs following workplace accidents. He observed that patients with amputations below the elbow got more use from prosthetic arms than those without the joint. He proposed developing an improved above-elbow prosthesis. The company supported his idea, hoping its fruition would help injured policyholders return to work.

Glimcher flew to the Soviet Union to inspect a myoelectric hand—a prosthesis that used electrical signals from the wearer's residual muscles to control movement.

Then, in the early 1960s, fate again intervened. Glimcher was serving as an HMS associate professor of orthopedic surgery at Massachusetts General Hospital. One of his patients, admitted with a broken hip, was MIT professor Norbert Wiener, the "father of cybernetics." Conversations between the two soon became discussions of human-machine interfaces. They started collaborating; others joined their effort, notably MIT's Robert Mann, a rocket scientist who had shifted focus to alleviating physical disabilities.

In 1968, the team unveiled its prototype for the first above-elbow myoelectric arm.

The Boston Arm activated when the wearer tried to move their missing lower arm. The biceps or triceps muscle in their residual limb generated a faint electrical signal that was amplified by electrodes taped to the skin and sent to a motor inside the prosthesis. The motor, powered by a battery pack worn on a belt, turned a screw that bent or straightened the artificial elbow.

The arm further broke precedent by offering dynamic speed, acceleration, and force. The elbow bent faster if it received a bigger jolt from the biceps, while so-called strain gauges urged the muscles in the residual limb to work harder to lift heavier objects. The prosthesis ended in a hook controlled by hunching the shoulder.

The Boston Arm took minutes to learn instead of the weeks required by contemporary cable-and-harness mechanical arms, which forced wearers to contort their bodies to operate.

News outlets hailed the innovation as Vietnam War veterans streamed home with upper-limb amputations. There was talk of providing Boston Arms to survivors of polio and thalidomide-induced birth defects. Laurie Glimcher, MD '76, president and CEO of the Dana-Farber Cancer Institute, recalls her father appearing on television and in newspapers.

"I think the Boston Arm reflected my dad's love of discovery and appetite for going in new directions," she says. "He had a willingness to try new things and take big risks, even if there was a chance he'd fail."

"What's the point of living," she adds, "if you're not trying something important?"

Melvin Glimcher and colleagues achieved a marketable version of the arm in 1973. The device wasn't perfect—some users found it heavy, bulky, and noisy—and fewer than a thousand were ultimately sold. More influential than the arm itself, however, were the principles behind its use of natural muscle signals. The concept inspired a generation of myoelectric prostheses. HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



Life and Limb

BY STEPHANIE DUTCHEN

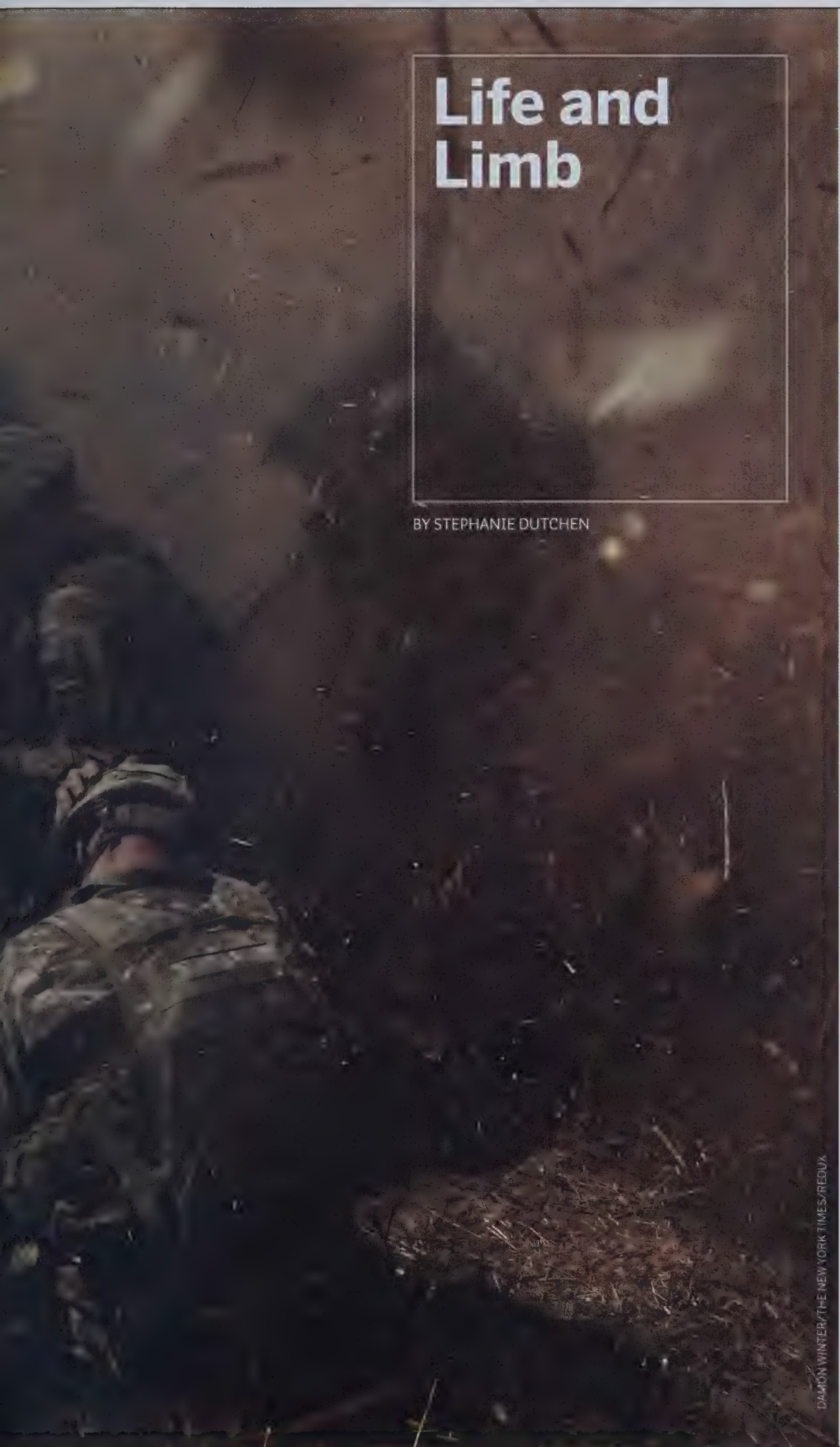
"You won't see World War II veterans with these injuries. You won't really see Korea or Vietnam veterans with these injuries," says Gregory Galeazzi. "Plenty of them got them; they just didn't survive them. Even though medicine has advanced, the majority of people who get these injuries still die on the battlefield."

"But for a select few," he adds, "they're able to piece us back together. They send us out to be socially active and return to the workforce."

Galeazzi, MD 2021, was a captain in the U.S. Army when he became one of the select few. During a routine patrol in Afghanistan's Kandahar Province in May 2011, a roadside bomb blew off both his legs and nearly severed his right arm at the shoulder. Without the swift action of his fellow soldiers, who applied tourniquets and rushed their semiconscious platoon leader into a medevac, Galeazzi would have perished.

Instead, after more than fifty surgeries and hundreds of hours of physical therapy, Galeazzi is completing his first year as a medical student at HMS.

The estimated 1,800 U.S. military amputees returning home from recent conflicts in Iraq and Afghanistan have been injured to an extent rarely seen before. Although the technical sophistication of prostheses has grown over the centuries, artificial limbs have yet to attain the capabilities of natural ones. To support work toward that goal, the Department of Veterans Affairs and the Department of Defense fund the lion's share of prosthetics research in the United States.



DAMON WINTER/THE NEW YORK TIMES/REDUX

Soldiers in the First Battalion, 87th Infantry, provide care to a wounded member of their group during a dust storm in Kunduz, Afghanistan.

While Galeazzi attends class

and clinic, scientists and clinicians throughout the HMS community are furthering the national effort by engineering prosthetic arms and legs that behave more like natural ones, pioneering brain-machine interfaces that create more intuitive connections between the nervous system and the prosthesis, and developing surgical techniques that allow for unprecedented prosthesis control and sensory feedback. Their work could benefit not only veterans but the other 98 percent of the 2 million people in the United States with limb loss due to diabetes, congenital conditions, cancer, and trauma, including accidents.

Perspective Shift

As innovations move from investigational stages to approval by the U.S. Food and Drug Administration, the broadening menu of options for amputees is changing millennia of clinical thinking.

"Historically, amputation has been viewed in the medical realm as a failure," says Matthew Carty, an HMS associate professor of surgery at Brigham and Women's Hospital, who is pushing the frontiers of amputation techniques and limb transplantation. "We need to talk about it as a reconstructive procedure and even a form of limb salvage. Physicians and patients need to consider the fact that amputation may be a faster and more effective pathway to better function and better life."

"The biggest change I've seen in recent years is the societal understanding that losing a limb is not the end," says David Crandell, an HMS assistant professor of physical medicine and rehabilitation at Spaulding Rehabilitation Hospital. Crandell managed the care of fifteen patients who underwent amputations following the 2013 Boston Marathon bombing. "People accept that technology can be part of the solution."

In Search of the Natural

Because of his battlefield injuries, Galeazzi ended up with two transfemoral—above the knee, through the femur—amputations. Doctors salvaged his arm and fused the elbow. He worked up to wearing prosthetic legs for a few hours each day until a series of health setbacks and the demands of premedical studies derailed his progress. He lost so much bone density in his hips and spine that he fractured two vertebrae in a fall in early 2017. Now he uses a wheelchair, and he's concerned that his reduced physical activity will affect his overall fitness.

"It took a ridiculous amount of energy to move those prostheses around," he says. "I was sweating just going from the couch to the bathroom and back."

Amputees confront dozens of potential health complications, from muscle atrophy and residual-limb infection, to low back pain and osteoarthritis from unnatural movement, to cardiovascular and metabolic disease from inactivity. Amputees who lose limbs in sudden events, losses known as traumatic amputations, often struggle with additional serious injuries, such as hearing damage, burns, and traumatic brain injury.

Developers of modern prostheses aim to alleviate some of these consequences and reduce pain by better mimicking the body's natural biomechanics and improving walking efficiency. Experts estimate, for example, that walking with a traditional prosthesis takes about twice as much effort and is one-third slower than walking on two natural legs. Each step jars the body and dissipates energy by sending it into the ground rather than helping it rebound into the body. The advent of springy modern materials like carbon fiber started returning some of that energy to the wearer. Moreover, in the past fifteen years robotic components have begun to "restore a physiological pattern of motion," says Paolo Bonato, an HMS associate professor of physical medicine and rehabilitation at Spaulding and director of the hospital's Motion Analysis Laboratory.

One prothesis with robotic components, the PowerFoot BiOM, was created by Hugh Herr, PhD '98, an HMS lecturer on physical medicine and rehabilitation at Spaulding and director of the MIT Media Lab's Biomechatronics group. Bonato was involved in testing of it.

When an amputee steps down on this bionic prosthesis, springs that mimic tendons compress and store energy; when the wearer pushes off the ground, a battery-powered motor taps that stored energy and, like a muscle, propels the user forward with twice the energy of a natural leg. The device, which melds biology with technology, was the first to allow the prosthetic foot to flex in a physiological manner. It also incorporated microprocessors that adjust for speed and incline. Studies by Bonato and others



The Empower ankle

The United States reached its peak of battle-induced limb loss during the Civil War, when an estimated

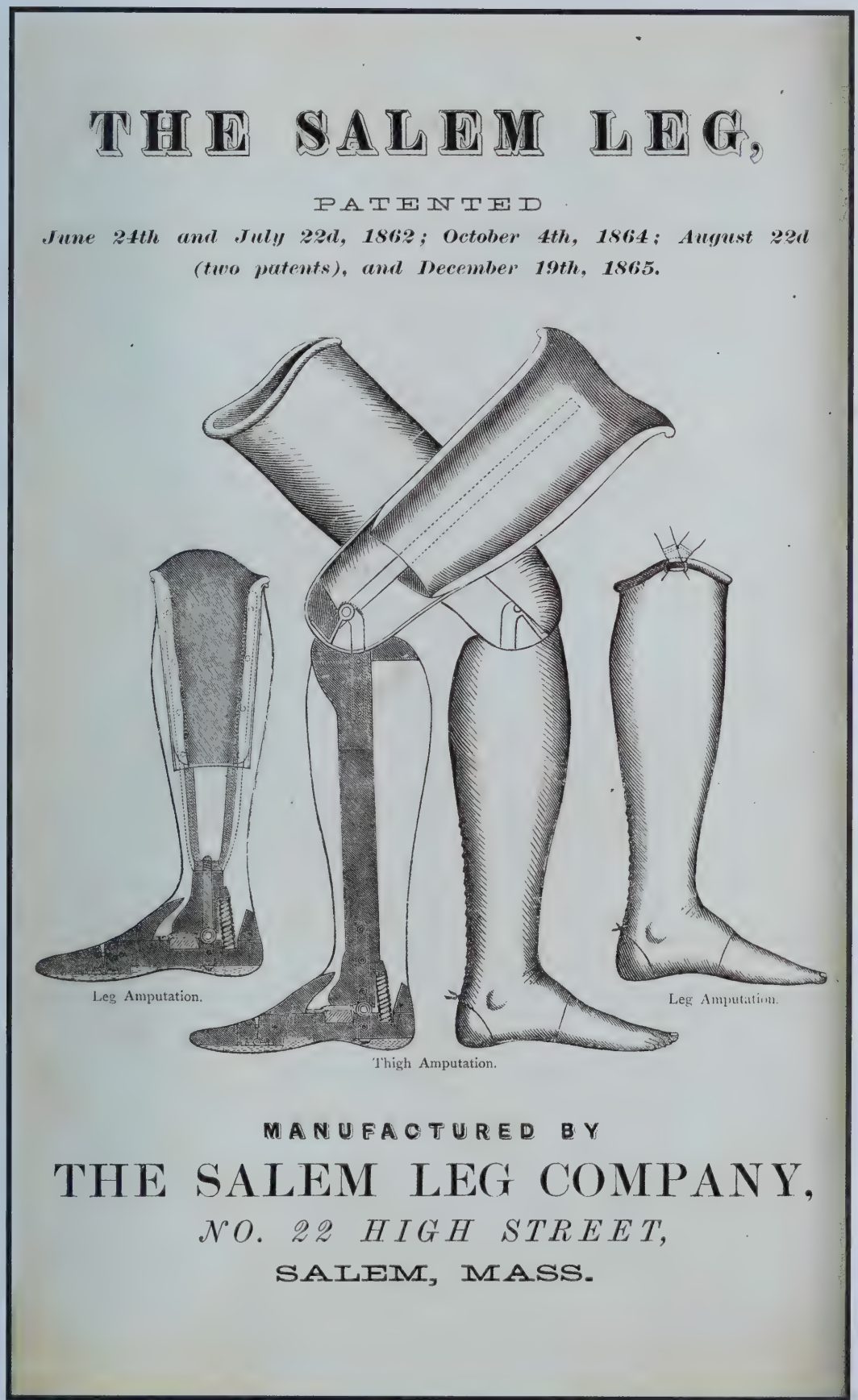
60,000

Union and Confederate soldiers underwent amputations; about

35,000

of them survived. Sheer numbers have fallen dramatically since then, but modern technology has created a new problem: It protects vital organs yet leaves limbs vulnerable to ever-more-destructive bullets and explosives.

IMAGE COURTESY OF OTTOBOCK



indicate that the prosthesis, marketed as the Empower ankle, improves walkers' balance, speed, and energy expenditure.

"Imagine you're forced to walk around in clunky, stiff cowboy boots, and then suddenly you're given lightweight Nikes and you can use your ankles again," says Herr, who uses the Empower ankle. "It's as distinct as going through the airport and hitting the moving walkway. It's exhilarating." Herr has been a world leader in bionic limb development since he lost both legs below the knee to frostbite suffered while mountain climbing in 1982.

Herr's group continues to collaborate with Bonato's to conduct complex analyses of human movement and energy expenditure, both to inform limb design and to gauge the success of those designs. Sometimes that means generating data on the intricate mechanics of a knee or studying muscle synergies in a reaching arm. More often, it involves measuring and modeling patient kinetics in the lab or sending patients home with wearable sensors to determine how well their prostheses work for them.

Not only will analyses inform the next generation of prosthetic limbs, but evidence of their health benefits could also expand access to them.

Restricted Movement

As medical director of the amputee care and adaptive sports programs at Spaulding, Crandell has seen his share of insurance denials for high-end prostheses. He chafes at some of the decisions on who deserves the best technology.

"Function and fairness are real societal issues," he says.

When a computerized, battery-powered titanium leg can cost $75,000, only about 15 percent of amputees in the country, main-

Following the Civil War, the artificial legs manufactured by the Salem Leg Company were recommended for Army use by the U.S. government. The company's president was Edward Brooks Peirson, Class of 1844.



ly those with amputations covered by VA or workers' compensation policies, have a chance of having the cost covered. That group, however, is far outnumbered by the 54 percent of U.S. amputees who, according to the Amputee Coalition, have lost limbs to diabetes and other vascular diseases.

So far, people with diabetes who have had a lower-limb amputation, often older and in poor health, are not considered good candidates for advanced prostheses. Crandell and Bonato challenge this view. They're experimenting with providing such patients with the best available technology, hoping that an easier-to-use prosthesis will encourage them to move more. If the program reduces complications such as second amputations, which occur in about 60 percent of people who lose one foot to diabetes, the researchers think insurance companies might reconsider their calculations.

Their hope may not be misplaced. Herr and colleagues nationwide recently got the U.S. Centers for Medicare & Medicaid Services to create a reimbursement code for bionic prostheses. The scientists plan to gather more data demonstrating improved gait and health to convince CMS to finalize coverage and pricing.

By Leaps and Bounds

Just before Darth Vader delivers shocking news to Luke about the Skywalker family tree in *Star Wars: The Empire Strikes Back*, he slices off Luke's hand with a lightsaber. Vader's revelation seems more traumatic for Luke than the loss of an extremity. It helps that he's quickly fitted with a lifelike bionic prosthesis, one so sensitive it can detect the prick of a needle.

The scene made a lasting impression on Crandell, who first saw the movie while in high school. The future the scene depicted may, in fact, be near. "I can't prescribe it yet, but I think the capacity for sensory feedback will exist in upper-limb prostheses in the next five years," Crandell says.

Although upper-limb prostheses have had their breakthroughs in the past half-century, they largely haven't progressed beyond hook hands. Amputees still give up on them at significantly higher rates than they do on legs. To close that gap, since 2008 DARPA has put more than $100 million into its Revolutionizing Prosthetics program for projects that focus on upper-limb development. That effort produced the DEKA Arm, renamed the LUKE Arm in honor of Skywalker. Approved by the FDA in 2014, the motor-powered above-elbow prosthesis has 10 degrees of freedom, six different hand grips, sensor-assisted feedback on grip strength, and the capacity to respond to wearer needs by moving multiple powered parts simultaneously rather than sequentially. Researchers are exploring new ways to control the DEKA Arm; HMS engineers are using it in brain–machine studies. A second arm being funded by DARPA uses electrodes implanted in both the brain and the residual limb to attempt neural control and sensory feedback.

At Spaulding, Bonato is collaborating with colleagues at Northeastern University on the development of a National Science Foundation-funded prosthetic hand controlled by a combination of muscle signals from the residual limb and electrical activity in the brain, as captured by electrodes embedded in a cap. The team is also adding cameras to prosthetic arms and using image-processing software to create prosthetic hands that anticipate what the wearer wants to do.

"If I'm approaching a button," Bonato says. "I probably want to push it. You begin to narrow down the likely movements a person might want to perform."

For legs and arms, the higher the amputation occurs on the limb, the harder it is to restore full function.

For legs as well as arms, the higher the amputation occurs on the limb, the harder it is to restore full function.

"Knees and elbows make all the difference in the world," says Galeazzi.

A shorter residual limb has more prosthesis to haul around and fewer muscles and nerves with which to manipulate it. Multiple joints—elbow and wrist and fingers, or knee and ankle—must coordinate, and legs often need to coordinate with each other. The Herr lab is working on a power knee to join the Empower ankle as well as prosthetic leg enhancements that scan the terrain ahead and preemptively adjust power and angle.

"The blistering rate of miniaturization of cell phone and computer technology, with incredibly powerful microprocessor capabilities and accelerometers and so on, means engineers can pack a lot into the small space of a prosthesis," says surgeon Carty.

Re-enabling basic activities may not be enough as amputees demand higher performance from their prostheses. Adults and children are 3-D printing limbs with custom features like water guns and vital-sign monitors. Kids are building and programming modules made of Legos to make their bionic hands perform different tasks. Typically young and fit, traumatic amputees itch to dive back into their active lives. The number of amputee soldiers able to requalify for active service rose from 2 percent in the 1980s to 16.5 percent by 2010, according to a study in *The Journal of Trauma: Injury, Infection, and Critical Care*.

"A lot of elderly amputation patients just want to walk between the bed and the toilet," says Galeazzi. "We want to walk—and climb mountains, and snowboard, and run marathons, and surf. I've seen guys with the

"The blistering rate of miniaturization of cell phone and computer technology means engineers can pack a lot into the small space of a prosthesis."

most advanced prostheses on the market come back after a weekend with the things snapped in half. They tell their prosthetists, 'You have to do better.'"

Redirects

Although survival rates and prosthetic technologies have improved over the centuries, the surgical procedure for amputation has remained essentially the same.

"We see surgical manuals from the Civil War era and from a 2004 textbook and the surgical techniques are nearly identical," says Shriya Srinivasan, a PhD candidate in the MIT-Harvard Program in Health Sciences and Technology, who is based in the Herr lab.

The standard technique of cutting a cross-section through the soft tissues before sawing off the bone means that severed nerves in the residual limb become unmoored, firing confused signals and often forming painful growths, while muscles that normally act in concert get disconnected. This shattering of physiology also prevents patients from taking full advantage of sophisticated prostheses.

"We haven't asked much of the residual limb in the past," says Carty. "Today's technology demands more from it."

Carty has joined forces with Srinivasan, Herr, and others to develop an alternative technique that preserves more of the limb's normal tissue relationships. They started with below-knee amputations. Carty takes tendons from the amputated ankle, anchors them to the residual tibia, and uses them to stitch together the ends of two muscles from the front and back of the leg so that when one contracts, the other stretches, as would occur in a normal leg.

The nerves that supply these muscles send clearer signals than those in traditional amputation and can receive basic signals in return. Implanted electrodes facilitate cross-talk between muscles, nerves, and prosthesis.

The researchers named the procedure AMI (pronounced "Amy"), for agonist-antagonist myoneural interface. They published a proof of concept in rats in 2017 and have now performed the operation on six human patients. What they're seeing is promising. Patients have less pain and more natural function when using standard prostheses than do individuals with traditional amputations. Those who try advanced prostheses enjoy more intuitive control and greater range of motion. The procedure also restores a measure of proprioception, giving patients who wear a prosthesis a sense of its position without having to look. The team hopes it will also reduce phantom-limb pain.

Herr recalls the moment when the first AMI recipient attempted stairs in a lab test. The toe of his Empower ankle automatically pointed down to meet each step.

"We were shocked," Herr says. "He could feel the prosthetic joint, and his brain and spinal cord knew what to do."

Carty says the AMI technique may be able to be done as revision surgery in old amputations or in traumatic amputations. The main limitations are that it can't be performed on patients with nerve or vascular problems, such as diabetes. Because the procedure doesn't involve any new or difficult surgical techniques, Carty is optimistic that it could be broadly adopted.

Carty and colleagues now have a proposal in IRB review to combine AMI with osseointegration, an experimental technique that attaches a titanium post directly to the bone in the residual limb. In place of the typical sleeve-and-socket attachment worn over the limb, the prosthesis latches onto a portion of the post that extends through the skin. The technique, devised by a pioneer of dental implants, Per-Ingvar Brånemark, has been undergoing tests with patients in Europe. In legs, osseointegration allows bone rather than soft tissue to bear the body's weight and transmits a better feel for what's underfoot. In arms and legs, the method could ease pain, reduce skin chafing and breakdown, and allow wearers to pursue activities that might cause a suction-adhered prosthesis to fall off. The main concern is risk of infection. The first U.S. trial to assess safety and feasibility began at the VA Salt Lake City Health Care System in 2015.

In legs, osseointegration allows bone rather than soft tissue to bear the body's weight.

Mind Meld

Some HMS researchers seek to link prosthesis control directly with the brain.

Leigh Hochberg, an HMS senior lecturer on neurology, part-time, and director of the Center for Neurotechnology and Neurorecovery at Massachusetts General Hospital who also holds appointments at Brown University and the Providence VA Medical Center in Rhode Island, is principal investigator on an investigational brain-computer interface called BrainGate, a technology that aims to restore communication between the brain and either external devices or muscles in patients with conditions such as spinal-cord injury, brain-stem stroke, and amyotrophic lateral sclerosis.

To achieve the interface, a small electrode chip is implanted in the participant's motor cortex, located at the "top" of the brain, to record the activity in a few dozen neurons. A small titanium pedestal attached to the skull conveys the neurons' low-microvolt signals, which are then amplified and sent to a computer, where algorithms decipher the participant's intention, for example, to move their hand "up and to the right."

"We see surgical manuals from the Civil War era and from a 2004 textbook and the surgical techniques are nearly identical."

The commands then get transmitted to a computer screen, a robotic or prosthetic arm not connected to the body, or to the participant's own arm muscles via a separate muscle stimulation system.

The technology is exciting but still in its early days, Hochberg and others note. To capture all the data being transferred, the titanium pedestal is thus far physically connected to a computer. Although these trials are taking place in participants' homes—exactly where, Hochberg says, clincially relevant technologies need to prove their utility—Hochberg and his BrainGate colleagues are actively working toward wireless implementation, a fully implantable version of the system, and improvements that would enable patients to use the system without research-team supervision.

Synthesis

Crandell sees more trainees each year who come into physical medicine and rehabilitation wanting to work with amputee populations. Interest also appears to be growing in other parts of the medical community. In addition to serving patient needs and driving new technologies, some are drawn to prosthetics development for the opportunity to collaborate with a range of specialists: mechanical, electrical, and tissue engineers; physicians and surgeons; neuroscientists, biologists, bioinformaticians, roboticists, nanotechnology specialists; prosthetists; and physical and occupational therapists.

While the bulk of projects are designed to improve devices and the way they interface with the body, others aim to reduce the need for prosthetic limbs. HMS surgeons have conducted successful single- and double-arm transplants. Carty now leads an effort to perform the nation's first lower-limb transplant. Stem cell scientists are pursuing regenerative medicine to one day grow biological limbs.

Significant as those changes would be, people who have already had amputations don't want to be left behind if they don't want or do not qualify for advanced procedures, or if they represent too small a market for prosthetics development. "We don't want to become the lost generation," says Galeazzi.

The outlook among HMS researchers is optimistic for all amputees for at least two reasons. First, no single solution will be right for everyone.

"We have to ask what will give each patient the highest level of function and quality of life: multiple surgeries for limb salvage, a prosthesis, a transplant?" says Carty.

Second, some hold that biology isn't necessarily better than synthetics.

"I'm not cellular- or tissue-centric," says Herr. "Prostheses are part of the human story. It's not something we'll eliminate when we figure out how to grow limbs with cells. In the future, many humans will be hybrid."

In many ways, we're already hybrid. Prostheses—devices that support or replace body parts or functions—include not only limbs but hearing aids, cochlear implants, eyeglasses, dentures, pacemakers, and artificial knees and hips. Massachusetts Eye and Ear ophthalmologist Claes Henrik Dohlman developed an artificial cornea, the Boston Keratoprosthesis, in 1992. Neurosurgeon Shelley Fried at Massachusetts General Hospital and the Boston VA is designing retinal implants. An HMS team at Beth Israel Deaconess Medical Center pioneered 3-D printed molds for "airway prostheses," stents that hold open patients' tracheas. Last year, Harvard engineers built artificial muscles for soft robots. As much as half the human body can be replaced right now with artificial components.

For his part, Galeazzi wants the option of switching between a wheelchair and prosthetic legs; the first helps him travel long distances, the second would make it easier for him to navigate narrow exam rooms.

Although prostheses and alternatives have come far, there's still ground to cover before every patient shares the sentiments of the amputee featured in "The One-Legged Man," a 1916 poem by English poet Siegfried Sassoon. After losing a limb in the Great War, the poem's narrator reflects in his elder years: "Thank God they had to amputate!" HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



Titanium is a light, lustrous metal that is highly resistant to corrosion, a property that makes it a good candidate for devices that are implanted in human tissue. It is as strong as steel but

45 percent lighter,

and twice as strong as aluminum but

60 percent heavier.

Initially discovered in 1791, it was first isolated in its pure form in 1901. Its name refers to the Titans in Greek mythology.



A detail of an above-knee prosthesis that is in development. The motor and its housing reflect some of what inspired its design: Japanese wood joinery techniques, ancient Americas sculpture, and sci-fi elements of modularity.



"As we march into this century, we're going to ask again and again what it means to be human. If you replaced all my limbs with synthetic bionics, am I still human? To me, the answer is absolutely 'yes.' Our design world can very much reflect who we are and what we hold dear. We should embed our values and our wishes and dreams into what we build."

—Hugh Herr, PhD '98, HMS lecturer on physical medicine and rehabilitation at Spaulding Rehabilitation Hospital, and director, Biomechatronics group, MIT Media Lab

Human Elements

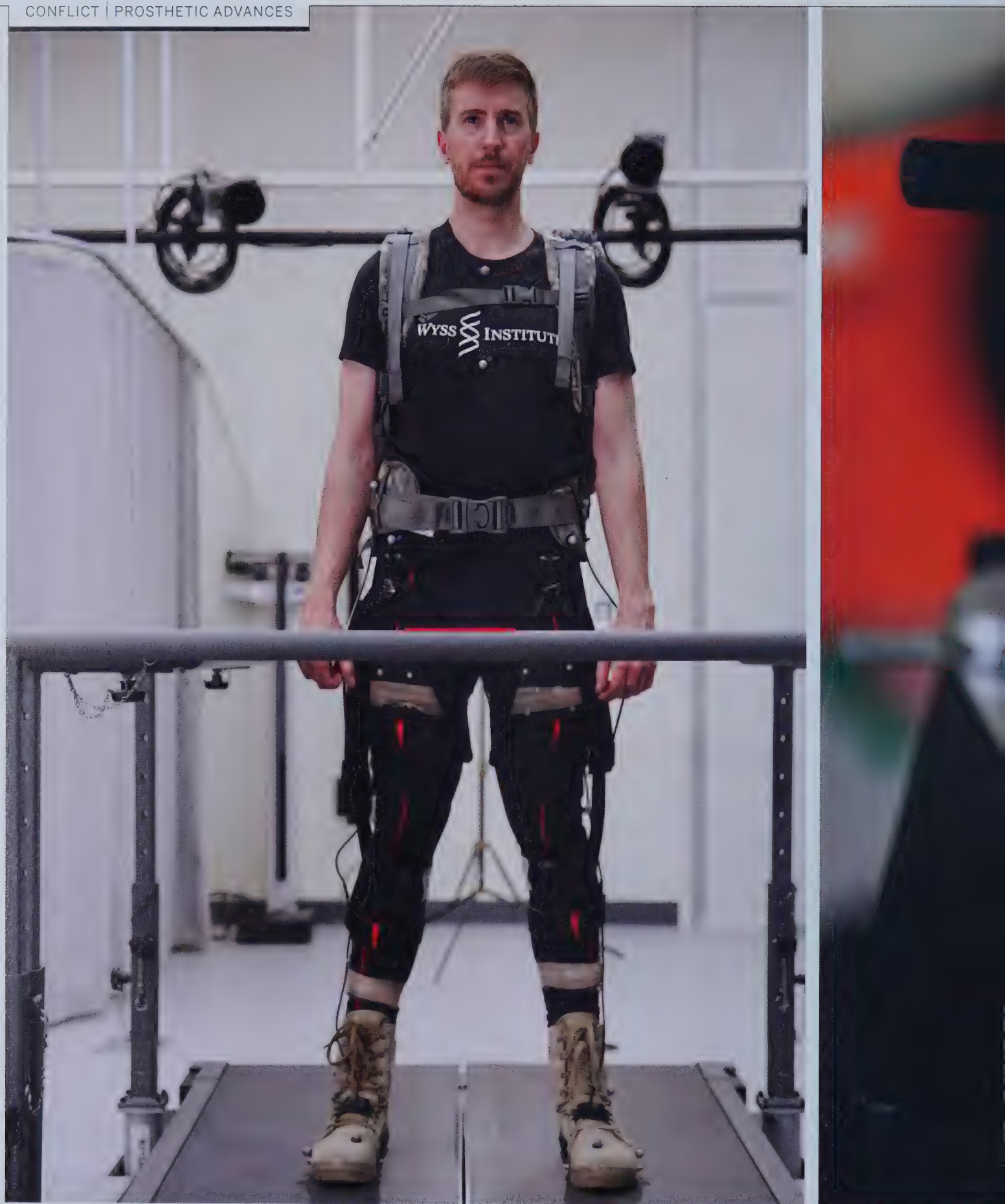
BY STEPHANIE DUTCHEN



In a prosthesis being developed for above-knee amputees, a single actuator serves as both knee and ankle while a custom motor-and-spring design mimics biological muscles and tendons. The leg is designed to improve range of motion, dynamic performance, power, and energy efficiency over that delivered by existing lower-limb prostheses while weighing no more than an average adult leg.



Although standard socket attachments are carefully fitted to the wearer's residual limb, they often cause pain as they scrape against bone and chafe skin. Biomechatronics researchers are working to design custom sockets that are stiff where an individual's limb is soft, and vice versa. To do this, the scientists capture a 360-degree image of a wearer's arm or leg, construct a mathematical model of its contours and tissue densities, then use a 3-D printer to construct a socket made of polymers that provide several different degrees of firmness.


WYSS INSTITUTE



Nerve fibers regrow in residual rat limbs following an experimental amputation technique that preserves more natural neuromuscular relationships than previously possible. HMS researchers are exploring embedded electrodes and optogenetic muscle stimulation to not only provide finer prosthesis control but also to deliver sensory feedback from the artificial limb.

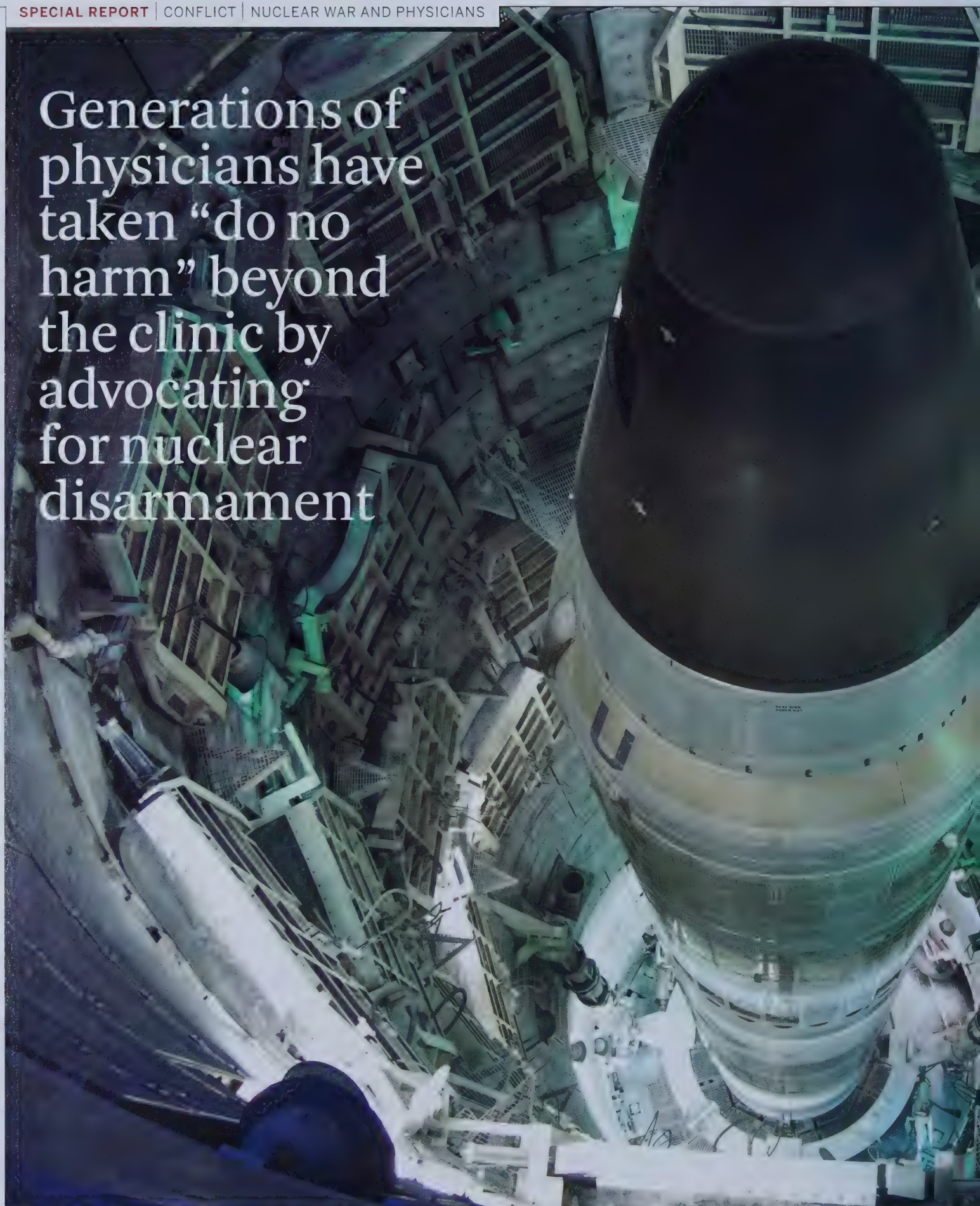
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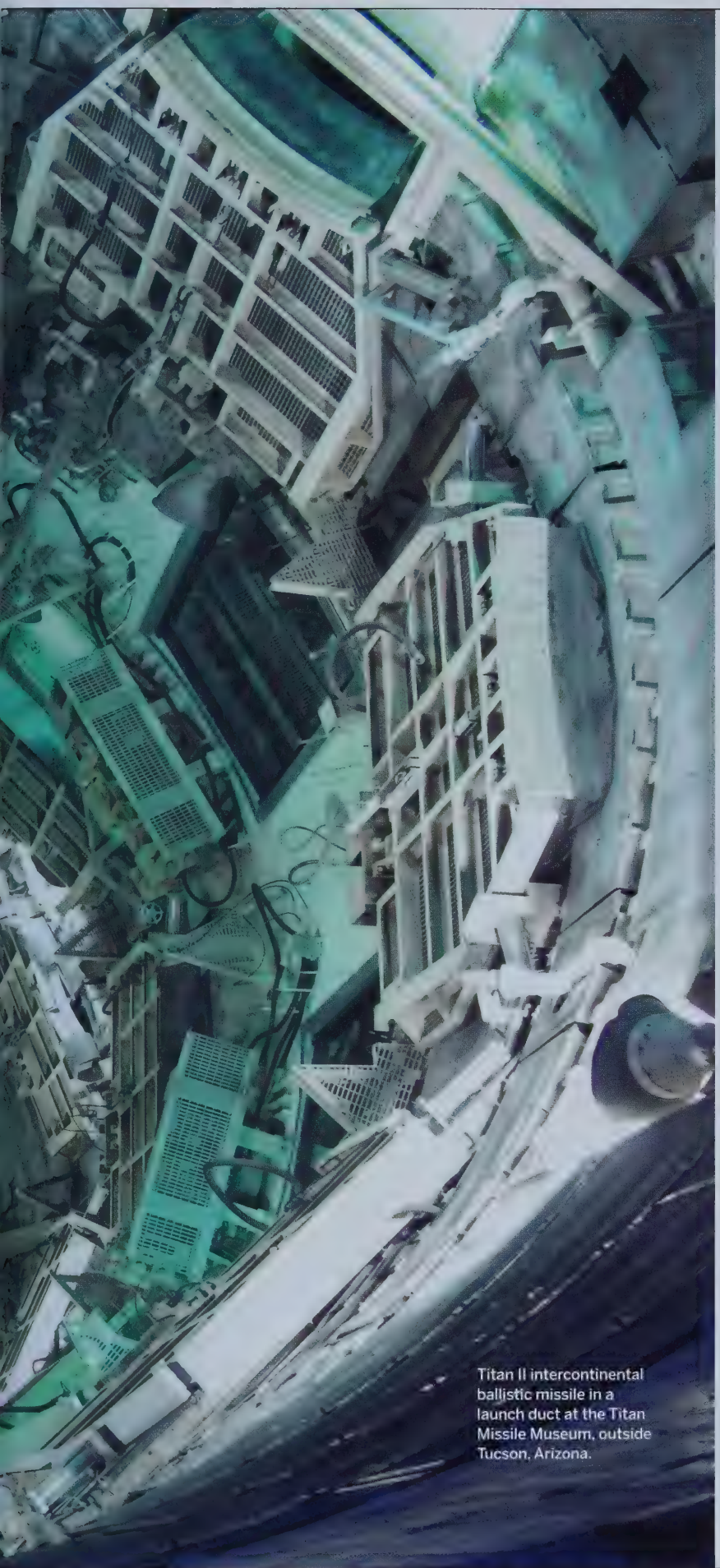


Hard exoskeletons and soft exosuits (far left, above, and below) can restore function for patients with limb weakness or paralysis resulting from injury or disease. They can also augment the performance of able-bodied individuals, such as soldiers who need to maintain their stamina while carrying heavy packs over long distances. Exosuits that deliver small forces to specific locations at key moments can help people with spinal-cord injury bend and extend their hands and help stroke survivors retrain muscles to correct for foot drop and other gait abnormalities.



Generations of physicians have taken "do no harm" beyond the clinic by advocating for nuclear disarmament





Titan II intercontinental ballistic missile in a launch duct at the Titan Missile Museum, outside Tucson, Arizona.

COURTESY OF THE TITAN MISSILE MUSEUM

Chain Reactions

BY JAKE MILLER

It's not uncommon for a physician to tell a patient that she's facing a health crisis. It's something Ira Helfand does regularly in his role as a primary care and urgent care physician in Springfield, Massachusetts. But outside of his clinical practice, Helfand talks more broadly about the troubling symptoms facing a different kind of patient: the global population.

As a longstanding leader of Physicians for Social Responsibility (PSR) and International Physicians for the Prevention of Nuclear War (IPPNW), and as a member of the steering committee of the International Campaign to Abolish Nuclear Weapons (ICAN), Helfand is often asked to talk about the dangers that nuclear weapons bring to global health. Whether addressing large audiences or discussing the issue one-on-one with an international leader, Helfand usually has to start by presenting the listener with a new, more realistic perspective on nuclear conflict.

"They feel they know," he says. "They're like young cigarette smokers who tell you, 'Doc, you don't have to talk about this. I know cigarettes are bad for me.'"

"But when I begin to spell out the details of what would happen in a nuclear attack, I can see their pupils dilate," he adds.

Helfand thinks it's critically important that physicians tell their patients, and the broader community, about the extraordinary danger of nuclear weapons.



"This is the greatest public health threat in the world today," he says, "and we, the medical community, are uniquely positioned to help people understand this."

Helfand is one in a long line of physicians who look outside the clinic to advocate on issues that could affect the health of the world's populations. The roots of this far-reaching activism can be traced to the fundamental "do no harm" pledge all physicians take as they begin their careers as healers. At HMS, this responsibility is augmented by the rich tradition of skepticism, empiricism, and leadership in which Harvard physicians are steeped.

Medical activists at HMS and elsewhere feel that if they speak publicly about the danger of nuclear conflict, they can mobilize people to take appropriate action to lessen that danger. If they don't speak, they worry, their silence will be as good as saying that no problem exists.

The Prepared Mind

The story may not be widely known, but HMS was the epicenter of the mid-century nuclear disarmament movement in the United States and, perhaps, globally, says Paula Michaels, an associate professor at Monash University in Melbourne, Australia. Michaels, who is researching the history of physician activism in the disarmament movement, has been drawing on the collections at the Francis A. Countway Library of Medicine for her work.

"There is a kind of collective amnesia around the role that physicians have played in the peace movement, and that they continue to play," Michaels says.

Part of the history Michaels worries will be forgotten took place in the early 1960s in Massachusetts, when a group of physicians and residents from HMS and a handful of other medical and research institutions in the Boston area began meeting for research and study sessions at the Newton home of Bernard Lown, then an assistant professor of medicine at the former Harvard School of Public Health.

Lown, a cardiologist, had been comfortably engaged in inventing the DC defibrillator while also researching causes and possible treatments for sudden cardiac death when a friend invited him to attend a speech by peace activist Philip Noel-Baker, recipient of the 1959 Nobel Peace Prize. Noel-Baker was to speak on the dangers of nuclear war.

Lown walked out of the event a changed man. "I realized that sudden nuclear death was even more important than sudden cardiac death. I felt compelled to do something about it."

Seated in the same living room where that ad hoc group began meeting more than five decades ago, Lown, now Professor of Cardiology Emeritus at the Harvard T.H. Chan School of Public Health and a retired senior physician at Brigham and Women's Hospital, still feels compelled to emphasize the dangers of nuclear weapons.

"A nuclear bomb is not just a bigger bomb," he says. "It's something else entirely. It kills everything, not just humans. And it pollutes everything. It leaves a residue of radiation that causes genetic changes, a pathology that is passed from generation to generation."

Local to Global

When the group of physicians began meeting, a nuclear war between the United States and the Soviet Union was considered likely, yet very little was known about what the real consequences of such a war would be. At their gatherings, the doctors discussed what they might do to understand and help raise awareness of the potentially catastrophic health effects of a nuclear war.

Together with Lown, several of the regular attendees—Victor Sidel, MD '57, who, at the time, was an HMS teaching fellow; H. Jack Geiger, then an instructor in preventive medicine, and David Nathan, MD '55, then an HMS research associate in medicine—decided to tackle the issue as only they could: as physician-scientists. They would research the medical ramifications of a nuclear explosion and then seek to publish their findings in a reputable journal. In addition, they would accomplish this collaboratively and collectively, now as members of a new group, Physicians for Social Responsibility.

They achieved their goal. The May 31, 1962, issue of *The New England Journal of Medicine* featured a series of papers on the medical consequences of nuclear conflict. Using Boston as their example, the papers summarized the medical and environmental consequences of a nuclear attack on the city and addressed the specific challenges that the local medical community would face in the aftermath of such an attack.

The attack scenario the researchers presented was a simplified version of what the Subcommittee on Radiation of the Joint Committee on Atomic Energy, a U.S. congressional committee, considered a likely estimate of the weapons that the Soviet Union would aim at Boston. One of the articles in the series laid out the human and ecologic effects of a thermonuclear attack involving ground-level explosions of an assumed 20-megaton bomb in Boston and an 8-megaton bomb at Hanscom Air Force Base in Bedford, Massachusetts, approximately 20 miles northwest of Boston.

Drawing on published data from the nuclear attacks on Japan and the fire-

BRUCE DAVIDSON/MAGNUM PHOTOS

Bernard Lown (left) and Soviet cardiologist Yevgeny Chazov, co-recipients of the 1985 Nobel Peace Prize, awarded to International Physicians for the Prevention of Nuclear War (IPPNW).

"A nuclear bomb is not just a bigger bomb. It leaves a residue of radiation that causes genetic changes, a pathology that is passed from generation to generation."

storms generated by conventional bombs in Hamburg, Germany, the researchers projected that "the area of total destruction, in which even the most heavily reinforced-concrete structures and deep blast shelters would be demolished, would have a radius of 4 miles. This would [include] … most of the medical facilities and personnel in the Boston area."

According to the researchers, if you lived in the metropolitan Boston area, a region that then had a population of between 3.3 and 3.7 million, you could be among the estimated two million people who would die immediately from the blast and heat generated from the explosion or among the additional one million who would be injured and in need of medical care.

People in shelters located within 15 miles of the blast center also would likely die either from being crushed by collapsing buildings or from asphyxiation as fires ignited by the blast consumed the oxygen in the shelters.

The researchers went on to detail additional medical concerns, such as the consequences of long-term radiation exposure.

Another paper in the series discussed the role physicians would have in such an attack. Authored by Lown, Sidel, and Geiger, the paper focused on the logistical, ethical, and moral challenges of treating those injured in the same hypothetical attack on Boston. How should physicians best respond to the challenges of caring for a million severely injured people?

"Regardless of his own professional training and convictions, the physician will daily face demands from patients for euthanasia on a scale and with an intensity unparalleled in his past experience," they wrote. "Neither the Hippocratic Oath, the published codes of ethics of the American Medical Association nor the personal morality on which every physician relies provides an easy answer to these questions."

"In fact," they continued, "a review of these trusted and cherished guides in the light of the problems of thermonuclear war makes them seem curiously and sadly obsolete, as if they reflected the human innocence of an earlier era."

Because of the devastating medical consequences of such an attack and the limited capacity of surviving physicians to respond effectively, the authors concluded that physicians "must also explore a new area of preventive medicine, the prevention of thermonuclear war."

In the aftermath of World War II, many physician-activist groups began testifying about the grim realities of nuclear weapons.

"There is a mythology," says Michaels, "that medicine and science are above politics or outside of politics, but in fact they are utterly entwined." Choosing to ask whether bomb shelters will help people survive or counting the number of doctors who will live to care for the wounded is a political act, she says, just as choosing not to ask those questions is a political act.

Preventive Medicine

Glimmers of how physicians could focus on preventive measures and political questions to promote the health of populations can be found in the mid-nineteenth-century writings of Rudolf Virchow, a Prussian physician. Virchow thought that improvements in social conditions would be much more effective than medical interventions in prolonging human life, an opinion that won him few friends in the medical establishment. Similarly, his political activities did little to endear him to Otto von Bismarck and others in the political structure: In 1869 he presented a motion in the Prussian parliament in which he noted that expenditures on education had stagnated because of excessive defense spending.

Between the two world wars, antiwar movements initiated by physicians sprang up in Europe. In the aftermath of World War II, many physician-activist groups began to turn their attention to testifying about the grim realities of nuclear weapons.

PSR's step onto the stage of medical activism continued these efforts, escalating the conversation to counter growing global tensions. That same mission went international when, in 1980, several U.S. and Soviet physicians banded together to form IPPNW. The U.S. founders were based at HMS: Lown, radiologist Herbert Abrams, psychiatrist Eric Chivian, MD '68, and cardiologist James Muller. Within five years of its founding, IPPNW had grown to include 145,000 members from affiliated physicians' organizations in forty countries. These members had come together "to explain the medical and scientific facts about nuclear war to policy makers and to the public." PSR in the United States became one of those affiliates.

Non-Nuclear Option

When the concept of nuclear winter was first introduced, physicists and climatologists predicted that a full-scale nuclear war between the United States and the Soviet Union would hurl enough soot and particulate matter skyward to darken the Northern Hemisphere, leading to crop-killing cold that might pose a threat to the very survival of humans.

"What we now understand is that a much more limited nuclear war could cause enough climate disruption to end civilization as we know it," Helfand says.

A 2012 report from IPPNW, *Nuclear Famine: Two Billion People at Risk?*, analyzed several years' worth of research on climate disruption and associated effects on agricultural output that would result from a limited and regional nuclear war.

Using a nuclear conflict between India and Pakistan as an example, research showed that firestorms would loft nearly 7 million metric tons of black carbon aerosol particles into the upper atmosphere, an amount of light-absorbing soot that would lead to climate effects with global ramifications: massive corn, wheat, and rice crop failures in the United States and China. The IPPNW report concluded that such an event could result in famines that would threaten the lives of more than 2 billion people worldwide.

Lown likes to point out how militarism, climate change, pollution, economics, and other societal factors are connected with one another and not only can lead to potentially catastrophic health effects but also drive the risk for nuclear conflict. He thinks that medical schools and physicians must continue to work hard to prevent these potential public health crises.

Helfand, too, says that physicians have an incredible opportunity to continue to contribute to change.

"It's very scary looking at this," he says. "It's not clear that we are going to successfully stop catastrophic climate change. It's not clear that we're going to successfully eliminate nuclear weapons and prevent nuclear war. But there's every reason to believe that we could be successful if we work very hard and do the right things."

Past achievements of these physician-activists indicate that Helfand may be correct. In 1984, IPPNW received the UNESCO Prize for Peace Education; a year later, it received the Nobel Peace Prize. In 2017, ICAN, a coalition of IPPNW and similar organizations, was awarded the Nobel Peace Prize for its work to galvanize global support for the Treaty on the Prohibition of Nuclear Weapons. HM

Jake Miller is a science writer in the HMS Office of Communications and External Relations.

in 5

A conversation with Galit Lahav, Chair, Department of Systems Biology



Your work occurs at the intersection of cancer biology and mathematics. What sparked your interest in this field?

Early on I realized it's important to me to work on a problem related to human disease, so the work my lab does to understand a gene that suppresses cancer is the type of work that keeps my inner fire burning.

But I also love numbers, solving complicated puzzles, and quantitative analysis, so the mathematical aspect of my work captivates me. The ability to bring these interests together to understand biology is powerful and satisfying. Systems biology is a fast-moving field that calls for the integration of many skills and much knowledge. I love that I can be a student of it forever.

As a systems biologist you profile the behavior and fate of individual cells. Why is this important?

In most research in biology, one takes a tumor, a group of cells, an organism, and looks at how the cells behave collectively; how, on average, they respond to treatment or react to certain genetic modifications. I'm fascinated by the outliers, the nonconformists.

In cancer, there is a problem known as fractional killing—you kill most of a tumor's cells, but a small percentage survive. We've focused on these surviving cells, hoping to understand what renders them impervious. Understanding their behavior will, ultimately, inform treatment approaches.

What is the next frontier in your work?

In our research, we zoom in on a cell, analyze genes or pathways in a quantitative way, and determine how they modulate the cell's behavior. But systems biology also includes working with "omics," huge amounts of data collected from DNA sequencing, RNA sequencing, and protein analysis. Right now, there is a gap between these two areas. I'd like to work toward linking our mechanistically driven quantitative science with big data efforts: specifically, to combine dynamical measurements at the single-cell level with measures of a cell's entire proteomics, transcriptomics, and genomics. In my mind, this powerful combination is the next frontier of systems biology.

One of your passions is faculty development. What advice would you give to junior faculty and young scientists?

My first advice would be to grow slowly—to take the time to find the right people in order to build an outstanding lab. Second, realize that the first years can be overwhelming and chaotic. Find people to talk with, share experiences with, and get advice from. These social interactions are really important, especially during the uncertain years as junior faculty. Finally, stay true to yourself. I think it's important to remember that you were chosen because you bring something unique. Allow yourself to take risks, to identify your path, and, most importantly, to enjoy it!

You are committed to increasing gender equality in biomedicine and to cultivating female leadership. Academia has made progress on these fronts, but what are some of the areas where it lags?

There's still a mind shift that needs to occur. There is this misconception that when you're in science you have to think about science all the time, that everything else gets in the way. This notion can be particularly pernicious for women scientists. We need to internalize the message that having a rich, full life outside of the lab actually benefits us as scientists. I know this because, as a mother of twins, I have experienced this firsthand.

This is not just about gender diversity. In science, we solve astoundingly complex problems, and to do so, we need diversity in all of its forms. It's not just the right thing to do, it's the wise thing to do. —*Ekaterina Pesheva*

Past wartime observations inform current understanding of post-traumatic stress disorder

Nostalgia, soldier's heart, railway spine, neurocirculatory asthenia, shell shock, war neurosis, battle fatigue. Follow the names for the condition we now call post-traumatic stress disorder, and you'll trace the history of medical thinking regarding battle-induced trauma, from physiological and psychological models to a combined model, neuropsychiatry.

World War I made shell shock a household word, and even one hundred years after the end of that war, the term is still used as a synonym for stunned. Elmer Ernest (E. E.) Southard, MD 1901, in *Shell-shock and other neuropsychiatric problems*, a prodigious feat of cataloging published in 1919, served the medical profession by editing and compiling nearly 600 cases of battle-related trauma, drawing from "the literature of the belligerents, 1914-1917, English, French, Italian, Russian, and—so far as available here—German and Austrian."

Intended as a training manual, the resulting casebook in "fields now collectively termed neuropsychiatry" reveals how wartime physicians were thinking about the condition as they encountered it. Southard hoped the book would prove useful in what he called reconstruction, or the mending of soldiers' post-war psyches.

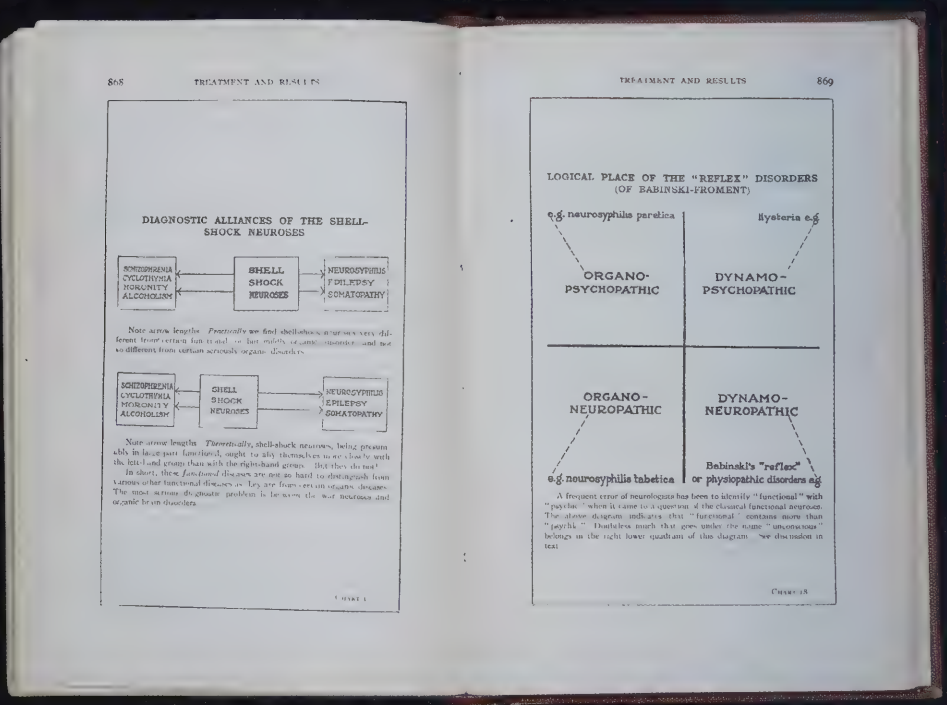
The work recognized the condition as a response to a violent event, but questions remained of contributing factors and whether the condition was more organic or functional, more physiologic or psychologic, more soma or psyche.

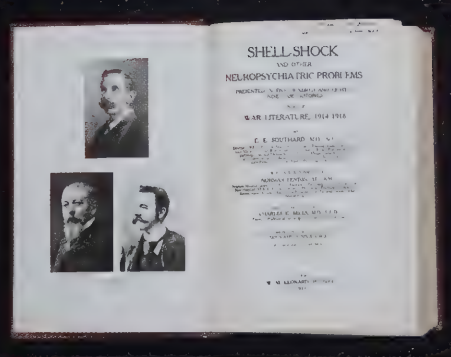
In Southard's time, it was recognized that no two people had the same reaction to the same traumatic event and that some of the variation in response had to do with predictive factors such as prior or existing disease, substance abuse, and psychosis. While these and other factors are still part of the clinical picture, we now know far more about the plasticity of the brain and how experiences can alter its structure and function.

The question of why some people suffer severe consequences after trauma while others do not has still not been adequately answered. Kerry Ressler, MD '97, PhD '97, an HMS professor of psychiatry at McLean Hospital, has been researching the role of resilience and coping—how a stressful event is appraised and the strategies used following the appraisal—in the range of responses to trauma and development of chronic PTSD.

Like Southard, Ressler and other researchers are searching for ways to lessen or prevent chronic PTSD. The work in resilience is yielding some insights, but, as Ressler wrote in a recent paper, "it remains unclear how coping strategies influence resilience and PTSD development in the acute aftermath of trauma."

—Susan Karcz





Elmer Ernest Southard's compendium of cases of battle-related trauma included diagrams in which he attempted to situate shell shock neuroses within the diagnostic constructs of his time.



Taralyn Tan

Class Prep

An idea leads to an evolution in post-graduate education in the basic sciences

BY CHRISTEN BROWNLEE

ON A WINTRY THURSDAY MORNING, Taralyn Tan, PhD '16, woke before the crack of dawn to prepare for a packed day.

After showering, feeding two hungry cats, and sipping some coffee, she headed over to the Warren Alpert Building on the HMS campus, where she sat in on the Discipline of Neuroscience class, a new foundational class in the School's graduate Program in Neuroscience (PiN). For three hours, she watched and listened, gauging how the curriculum changes she'd helped implement were working with students and faculty. As that class was wrapping up, she raced to the Boston Children's Hospital-based lab of Maxwell Heiman, an HMS assistant professor of genetics. Tan, who has a part-time postdoctoral fellowship, spent a couple of hours in the lab, ensuring that her investigations of the sex-based differences in a subset of roundworm brain cells remained on track. Then she was off to Cambridge to lead a neurobiology tutorial for Harvard College undergraduates on how to read and write about scientific literature.



Twelve

hours after that first sip of coffee, Tan went home—and settled in for a few hours of work developing materials for the PiN course website and mapping out the rest of her week.

"I have a bad habit of putting a lot of stuff on my plate," she says. "But I have only three years here, so I want to extract as much out of the time as I can."

Tan's full days reflect her unusual role: She's an HMS curriculum fellow, a "service in scholarship" role that, from all indications, exists only at HMS. Members of the School's current pool of ten fellows are PhDs in various fields, each fueled by a passion for improving education at the undergraduate or graduate level. The fellows are embedded for three years in different academic departments and tasked with using the latest pedagogical research to help revamp their department's curriculum. Tan works in the Department of Neurobiology.

The hands-on arrangement benefits the departments and the fellows. Each department gets a curriculum that reflects current thinking on what students in that discipline need to know, presented in a manner that addresses how today's students learn. In turn, each fellow gains knowledge and experience in teaching and administration and in undertaking and publishing their own educational research. By providing the fellows with a structured career opportunity, the School not only maintains a progressive, innovative curriculum in basic research but also cultivates the next generation of scholar-scientists who will work in higher education and shape how science is taught far beyond the HMS Quad.

Problem-Solving Skills

The Curriculum Fellows Program got its start just over a decade ago, when Randall King, MD '97, the Harry C. McKenzie Professor of Cell Biology; David Van Vactor, an HMS professor of cell biology; and other colleagues in the School's Department of Cell Biology identified a problem facing graduate education. At research-intensive graduate and medical schools like HMS, basic and applied sciences are such a priority that faculty often have little time and few resources to devote to developing best practices in pedagogy.



David Van Vactor (above, left) and Randall King

Although postdoctoral fellows are pivotal to pushing the boundaries of basic research in science, an equivalent impetus in science education or science education research is sometimes missing. The result: curricula lack a catalyst to spur innovation.

In 2007, as the incoming head of the PhD program in Biological and Biomedical Sciences, Van Vactor needed a way to fix this. Working with colleagues and teaching fellows, and with support from the School's dean and preclinical department chairs, he proposed the development of postdoctoral fellowship-like positions in which the incumbents would focus on education. Brought in for three-year terms, these curriculum fellows would use insights gleaned from pedagogical literature to help faculty revamp their curricula and training programs. This training, augmented with other educational and research opportunities, would help the fellows prepare for careers in education.

"In the same way that terrific, talented postdoctoral fellows in the laboratories here bring a lot of educational richness and hands-on energy to the research mission," says Van Vactor, "we expected the curriculum fellows to bring the equivalent to the enterprise of educational programming, teaching, and training."

Independent Study

Van Vactor, the program's director, and his colleagues in several departments brought in the first cohort of fellows in 2008. One

of these pioneers, Johanna Gutlerner, was hired as a fellow in the Department of Biological Chemistry and Molecular Pharmacology. Soon, however, she and the other fellows realized there were some bumps that needed to be ironed out in the fledgling effort. It was clear, she recalls, that much of what had been advertised about the fellowships was aspirational rather than actual. Yes, they would gain experience overhauling the various curricula, but there was little else earmarked for the fellows' development.

"There was no mentored teaching, no classroom observations, and no opportunities to do educational research unless we made them," says Gutlerner, interim associate dean for planning and administration for basic science, graduate education, and global programs at HMS; an HMS lecturer on biological chemistry and molecular pharmacology; and former co-director of the Curriculum Fellows Program. "That's when we came together and started making these positions into what everyone hoped they'd be."

With Van Vactor's help and with suggestions from other fellows in the program, Gutlerner wrote a detailed operations manual for the program, one that masqueraded as a polite list of demands. In it, the fellows requested a centralized space for work and for weekly meetings. These meetings would be akin to those held in research labs to discuss pedagogical literature and to present work for feedback and advice; ultimately, they became educational laboratories. The fellows also sought to ensure that 20 percent of their time would be protected for scholarship and career development.

Gutlerner wrote a detailed operations manual for the program, one that masqueraded as a polite list of demands.

Course List

Over the years, says Bradley Coleman, the current co-director of the program and an HMS lecturer on microbiology and immunobiology, the fellows have used some of their protected time to initiate improvements to the program to make it more useful to the fellows, to the HMS community, and to other schools. Curriculum fellows developed two classes—Teaching 100: The Theory of Science and Teaching, now required for all incoming program fellows, and Teaching 101: Bringing Effective Teaching Practices to Your Classroom. Teaching 101 is targeted for PhD students but also draws master's students, curriculum fellows, and postdocs or junior clinicians. Coleman co-leads Teaching 100 and was an instructor in Teaching 101 during his own curriculum fellowship in 2016 and again in 2017.

Other initiatives from the program fellows include a series of monthly pedagogy workshops for the HMS community and a seminar series that brings in speakers in the fields of teaching and learning. In addition, the fellows guide and mentor graduate students in the Science Education and Academic Leadership certificate program. The SEAL program allows participants to develop curricula, teach, and receive constructive feedback on their teaching.

By far the most common use of protected time, however, is to gain teaching experience. For Tan, this time has allowed her to develop and instruct a class for Harvard College students on sex differences in the brain. This exposure to teaching, she says, offers the fellows an avenue to pursue their passion to teach and gives them experience they can use when they enter the job market.

Training the fellows to be part of the modern workforce is a goal of the program. In 2013, in a commentary on the program in *Cell*, Van Vactor and Gutlerner pointed out the need to move from the content-driven curriculum that characterized life-science graduate education toward an interdisciplinary, concept-driven curriculum. The change is not one they alone called for; it's one espoused by oversight bodies such as the Association of American Medical Colleges, the American Association for the Advancement of Science, and the National Research Council. That evolution, Van Vactor and Gutlerner argued, is taking place in the School's Curriculum Fellows Program. With its emphasis on developing technical and communication skills, integrating science curricula, and strengthening the fellows' understanding of experimental design and quantitative methodology, the program is an agent for the very change sought, and needed, for science education and educators.

Special Project

At the heart of the Curriculum Fellows Program is the work that each fellow does to improve and update the curriculum of the department that hired them. Rosalind Segal, an HMS professor of neurobiology and the faculty member who hired Tan into PiN, says that before Tan arrived, the neurobiology curriculum needed a complete overhaul. There was significant redundancy in the core required courses, and these courses needed to be appropriate for students coming from the variety of disciplines, including biology, computer science, and engineering, that merge in neuroscience.

Segal says Tan was especially qualified to help develop a new curriculum for the program; she had been a graduate student in PiN before becoming a curriculum fellow.

After assessing the program's curriculum, Tan worked with PiN faculty to develop a class that combined and restructured the content from four previous classes. She continues to help develop both classroom lectures and online course material. Tan also assisted in designing a new comparative neuroanatomy course and is working on developing several other new neurobiology courses.

"No new class is perfect," Segal admits, "but Tari's work has come close."

See, Do, Teach

Since its inception, the Curriculum Fellows Program has welcomed nearly thirty fellows into the program. As the program has matured, fellows have become more ambitious and have moved beyond doing work only for their department mentors, their students, and themselves, to undertaking work that benefits the broader science education field. Several fellows have published their research, and Van Vactor says that he and other program leaders encourage the fellows to publish the results of changes they've been implementing in the classroom.

Some of the program's alumni have gone on to faculty positions at small liberal arts colleges or large research institutions. Others, like Gutlerner, have filled administrative positions overseeing areas such as faculty training, curriculum development, and research planning at universities or educational organizations.

According to Van Vactor, the Curriculum Fellows Program has evolved to play a special role at HMS and, possibly, across the nation. The program is pivotal to advancing pedagogy in graduate education, and it trains those who will themselves train the scientists of tomorrow.

"We're already an important catalyst in training the scientists and inventors of the future," Van Vactor says. "We'll keep working to make that future bright."

Christen Brownlee is a Massachusetts-based science writer.



Student Life

Meet Chelsea Messinger, MD 2020, a second-year student at HMS. Like many of her peers, Messinger is packing as much as she can into her years at the School, seeking both to learn and to share the support and community she's found at HMS.

In addition to learning about patient care in HMS-affiliated hospitals, Messinger is part of the student-administered Crimson Care Collaborative at the Massachusetts General Hospital-Internal Medical Associates site, where she regularly helps care for patients who face barriers to accessing routine health care. She also volunteers with the Boston Health Care for the Homeless Program, where she assists in providing care to people who come to the program's clinics and, together with others from the program, in bringing health care directly to vulnerable individuals living on Boston streets.

As a student in the Harvard/MIT MD-PhD Program, Messinger is researching the epidemiology of preeclampsia and birth defects as she works toward her doctorate in epidemiology from the Harvard T.H. Chan School of Public Health. Messinger's interest in reproductive health began in her undergraduate years at Yale University and grew during a post-baccalaureate year as a Fulbright Research Scholar in Malaysia, where she carried out research on influenza during pregnancy. After she graduates from HMS, Messinger hopes to pursue residency training in internal medicine or obstetrics and gynecology before beginning a career as an academic physician-scientist focusing on the links between reproductive health and chronic diseases.

When not in the classroom, in the clinic, or undertaking research for her PhD, Messinger can be found mentoring Harvard College students as part of Harvard's Women in STEM (WiSTEM) Program and serving on the HMS LCME Student Leadership Team, which is helping the School prepare for its reaccreditation review by the Liaison Committee on Medical Education.

Messinger says that she knows her decision to pursue both medicine and public health is right for her. "My experiences working and volunteering in clinical settings reaffirm my desire to have a positive impact on the lives of individual patients. Meanwhile, my public health research enables me to ask questions that can lead to a greater understanding of medical problems, and to improvements in the health of populations."







Chelsea Messinger's rich and varied days at HMS include running along the Charles River, serving as a mentor in Harvard's Women in STEM (WiSTEM) Program, meeting with fellow students to discuss patient care, and helping to deliver health care to the homeless in Boston.





From the Ground, Up

HMS graduates pursue careers in a spectrum of fields. Rarely, however, do they become cobblers.

Casey Kerrigan was still a student at HMS when she realized that medicine didn't have a solid grasp on the mechanics of something as basic as walking. She became intrigued by gait. That fascination bloomed into a research interest when, following her presentation of a serious stroke case during her rotation at the VA Medical Center in West Roxbury, Martin Samuels, then an associate professor of neurology at Children's Hospital Boston, encouraged her to explore physical medicine for solutions to the problems she described in her patient's care options.

Kerrigan's subsequent research focused on knee osteoarthritis and gait mechanics, resulting in a landmark 1998 *Lancet* paper on the risks of wearing high heels. Her study was the first to suggest that wearing high heels alters the normal function of the ankle and causes torque in knee and hip joints, a twisting, she found, that contributes to the development of knee osteoarthritis. Osteoarthritis of the knee disproportionately affects women and is a leading cause of physical disability in older adults.

Kerrigan's interest in function then moved to form; she began developing concepts for low-impact footwear. Now, her company, OESH, manufactures "evidence-based footwear" that places less stress on joints to help reduce knee, hip, and foot pain. She was recently awarded a National Science Foundation phase 2 innovation grant to finish development of the specialized 3-D printing technology Kerrigan uses to manufacture the shoes. She has been designing shoes and sandals for women since 2011, and now designs for men as well.

During her first year at HMS, Kerrigan missed the one lecture on gait, an incongruity not lost on her. She says the biggest surprise of her career is that, unlike the offspring in the adage about cobblers, her children do not go barefoot. But those three young women don't wear high heels, either. —*Susan Karcz*

Casey Kerrigan, MD '87 • Chair, OESH Shoes • Charlottesville, Virginia

A Backward Glance

Recollections, reverent and otherwise, from a member of the Class of 1945

BY GIULIO D'ANGIO



When I was a student, Elliott Carr Cutler, MD 1913, was the Moseley Professor of Surgery at HMS and surgeon-in-chief at what was then the Peter Bent Brigham Hospital. He had been a brigadier general in the U.S. Army during World War II; when that war ended, he returned to the Brigham. A talented, pioneering surgeon, which he would not deny, Cutler always spoke of himself in the third person and would address those of us who were in the Army as "soldier" when we served as his assistants in the operating room. He often boasted of the sensitivity of his fingers, claiming to have such discrimination of touch that, with one sweep of the blade, he could penetrate through the skin, fat, and muscle of the abdominal wall to attain the intact peritoneum.

One day, he was demonstrating that extraordinary facility to an audience of visiting surgeons who had packed the observation gallery. John Homans V, MD 1903, an iconoclastic, irrepressible, witty, honest, modest, but nonetheless brilliant surgeon who was also at the Brigham, had a habit of wandering from one OR to another between cases. This day, he happened in as Cutler announced to the gallery, "General Cutler will now expose the peritoneum!"

Sweep went the scalpel.

Homans looked in and, raising his voice, intoned, "General Cutler will now suture the gut!"

Homans, of the eponymous sign used in the diagnosis of deep venous thrombosis, was an innovative vascular surgeon who explored surgical approaches designed to prevent venous thrombosis in the lower leg from migrating to the lungs. He tried ligating leg veins first and then went higher and higher with his ligations until he reached the inferior vena cava. We students knew we would be asked about the details of the local anatomy if we scrubbed in on one of his cases. My turn came, and although I had studied with care the lay of the inferior vena cava as seen after a transabdominal approach, Homans, to my horror, elected to reach the inferior vena cava retroperitoneally. The patient, a very large man, was rolled onto his side. Homans paused, then turned to me and, pointing with a long Metzenbaum to something deep

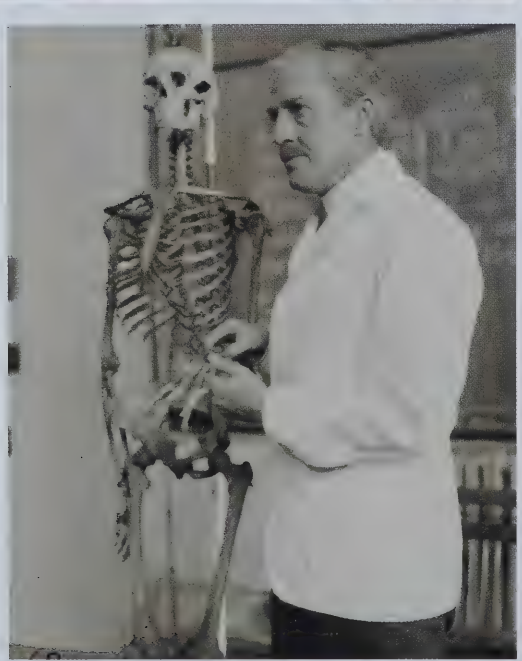
"General Cutler will now expose the peritoneum!"

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Elliott Carr Cutler (above, clockwise), John Homans V, and David Cheever



red in the depths of the wound, asked, "Whatzzat?" I peered into the narrow chasm of gore and uttered the words never to be said to Homans.

"Sir, I don't know."

"Umph!" he said. "Too bad. Hoped you would. Sure as hell, I don't know either." Then, typical of a great teacher, he said, "Let's find out."

Homans liked to tease his friend and classmate, David Cheever, MD 1901, also a Brigham surgeon. Compared with Homans, Cheever was quite a different person. He came from a prominent Boston family and was formal and correct in every way. Homans would remind his friend at the most inopportune moments—such as during a formal dinner party—about their forays as students into the fleshpots of Haymarket Square.

One day, Homans, having completed his first case, was making his rounds of the Brigham OR. He came across Cheever as he was starting a Halsted mastectomy. Homans went back to his OR for his second case and returned to Cheever's room, where the skin had been cleared and the lymphadenectomy was underway. Homans left, completed his third case, and returned to Cheever, who, not nearly through, was proceeding with his cell-by-cell dissection in the best Halsted tradition. At this point Homans erupted. "Davey! You'd better get that thing off before it metastasizes!"

Very different was the terrible-tempered William Quinby, MD 1902, a Brigham urologist who became that hospital's first chief of urology. He once congratulated me on having asked the most stupid question he had ever heard in his many years at Harvard. (I had

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asked him what, in his experience, was the most common cause of hematuria in adult males. He never answered my question.)

Quinby routinely threw his instruments as he changed from one clamp or forceps to another. One day, as he was operating on a patient under spinal anesthesia, a flying metal instrument landed on the patient's nose. The patient angrily asked what had happened. Bland assurances and explanations hardly sufficed, but peace finally descended. Then Quinby, who was bent double out of the patient's line of sight, glowered up at my classmate, the second assistant, and said, "Next time, you catch it!"

S. Burt Wolbach, MD 1903, a professor of pathological anatomy at HMS and a superb researcher, was chief at both the Brigham and what was then Children's Hospital Boston. Though a Nebraskan, he adopted the persona of an Eastern establishment gentleman. He always wore a red boutonniere, for example. I found him a little forbidding—austere, aloof, and above the fray. A little pompous, too, to tell the truth.

He was a world authority on the pathophysiology of rickettsial diseases. Typhus was his specialty, and with good reason: He had been part of the international commission to bring that disease under control in the shambles of Eastern Europe after World War I. He was always punctual. One day, he arrived precisely on time for the lecture on typhoid fever he was scheduled to deliver to us. As I recall the details of that day, he lectured smoothly, although many points he made didn't seem quite right. But who were we to doubt this august professor? He left precisely on time, only to return quickly and ask, "Did I say typhoid? I meant typhus."

Then he left.

There are many stories from my nine months as a pediatric surgical intern at Children's, but two are especially memorable for me. The first has to do with a child who had limb pain. Our workup revealed severe scurvy. We asked the mother if she was giving him orange juice. "Oh yes," she replied. "And I boil it real good so it will be healthy for the wee one."

The outpatient department was the site of the second incident. A distraught mother had brought in her baby. She had been taking a rectal temperature with a glass thermometer, turned the child on his back, and the item disappeared. Fluoroscopy showed it right where it shouldn't be: in the sigmoid. I called anesthesia, and with the help of a short-acting anesthetic agent, set about removing the glass rod. I had visions of splintered glass lacerating the gut, so proceeded cautiously with and without an anoscope. I received plenty of advice, none of it useful, and tried various schemes: lavages, transabdominal pressure from above, different instruments, even a rubber-draped Allis clamp.

Nothing worked.

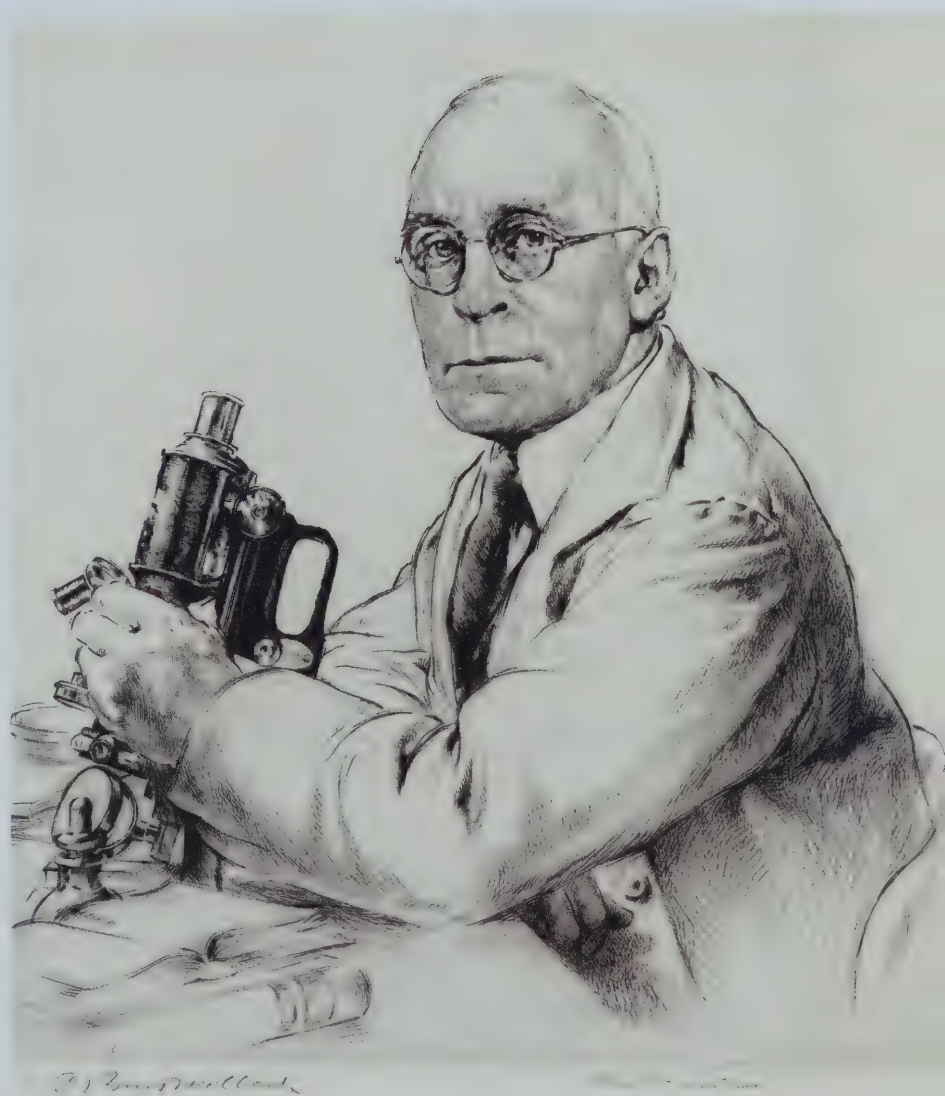
I finally decided to try my bare finger, hoping my fingernail would get enough purchase above the bulb. It did. Millimeter by millimeter, the item was teased down. Finally, after an hour or so of this drama, the thermometer emerged. I triumphantly picked up the infant and, brandishing the thermometer, approached the anxious mother.

"Oh! I see you got the thermometer out all right, doctor," she said. "What was the temperature?" HM

Giulio D'Angio, MD '45, is a retired radiologist, is a professor emeritus of radiation oncology at the Perelman Center for Advanced Medicine at the Hospital of the University of Pennsylvania. He lives in Philadelphia with his wife, Audrey.

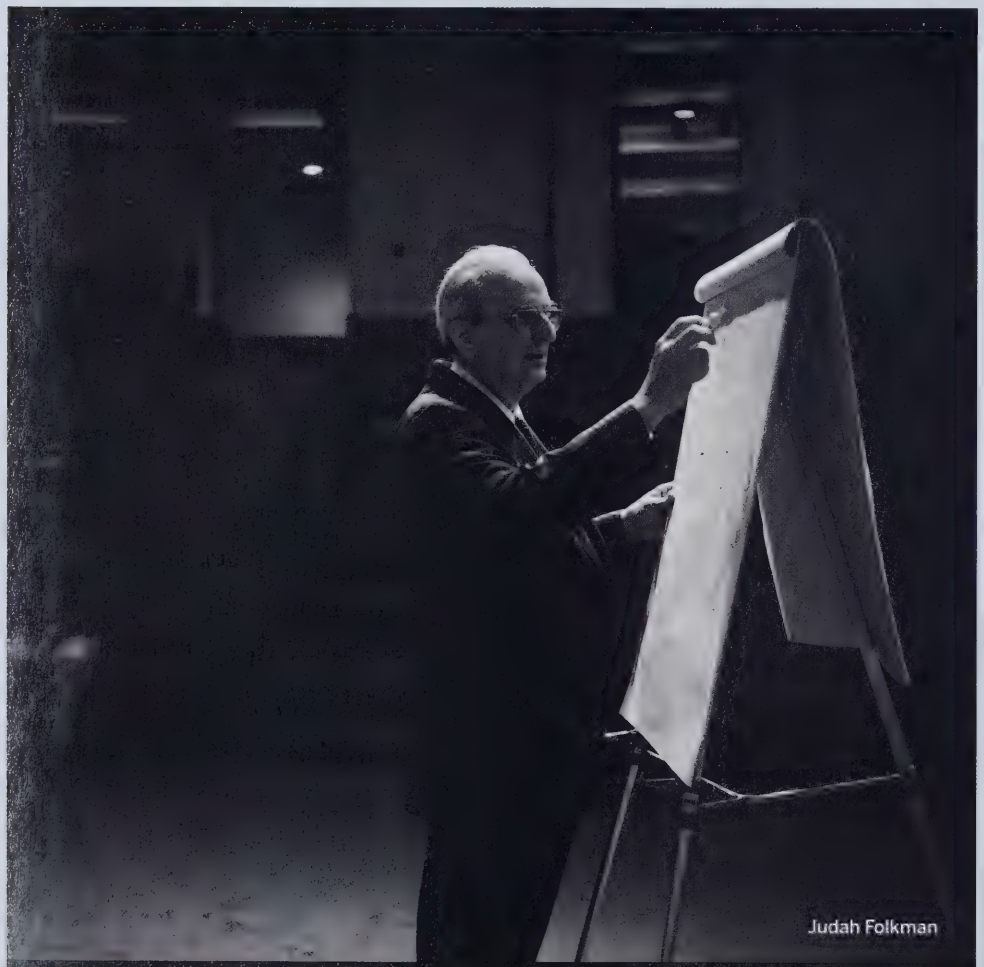


William Quinby (left) and S. Burt Wolbach



DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

Who was your **mentor** when you were an HMS student, and how did that person's advice **guide** you?



Judah Folkman

Joseph Ransohoff, PhD '69

Judah Folkman, MD '57, and I co-authored a book in 1968. It became the basis of the MIT-HMS medical bioengineering school. I met with the physicians at Massachusetts General Hospital, the former Peter Bent Brigham Hospital, and elsewhere who were working on everything from plutonium-powered artificial hearts, contact lenses, and prototypes of kidney dialysis membranes. Judah transcribed and edited my notes into the final book. Elkan Blout in biological chemistry was my thesis advisor.

Sean O'Connor, MD '82

John Hall and the other pediatric orthopedic surgeons at Boston Children's Hospital.

Ryan Chuang, MD '03

The other students around me were very inspiring.

Peter Zawadsky, MD '68

Charles A. Janeway, MD '69, was the physician-in-chief at Boston Children's. He successfully guided me through a period when I was not sure whether I wanted a career in pediatrics or internal medicine.

Howard Rubenstein, MD '57

My favorite mentors were Avram Goldstein, MD '43, professor of pharmacology and extracurricular teacher of biostatistics, and David Rutstein, MD '34, professor of public health. Both of these men had a grumpy exterior and were not particularly liked, let alone well-liked. But I loved them for their clarity of mind. If anyone taught me to be critical and analytical in my thinking, it was these two men. I still remember and admire them fondly. Has biostatistics made its way to the core curriculum yet?

Joan Leary Martinez, MD '66

The humility and generosity of William Castle, MD '21, inspired me. He was my hematology lab leader. One day he noticed that my lab stool was unsteady. The next lab day, he came with his tool kit and fixed my stool! I will never forget his thoughtfulness toward a preclinical medical student.

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Ellis Rolett, MD '55

I do not recall a specific mentor. However, several Mass General house staff, including Howard Rasmussen, MD '52, and Stephen Krane, were role models during my fourth-year medicine clerkship and were instrumental in my choosing internal medicine as a career.

John Griffin, MD '63

Daniel Federman, MD '53, the first-year tutor for four of us in 1963 and 1964, was an extraordinary introduction to HMS. He combined a profound knowledge of medicine with a special warmth of communication and gentleness that encouraged our entry into the somewhat threatening environment of first year. We loved him.

When he attended HMS gatherings in St. Louis and Atlanta, some of which I organized, he continued to guide me by example. He has had a lasting effect on my life and career.

Richard Peinert, MD '73

Hermann Lisco was always the person to go to with a problem. Mine was the second class of the "new" curriculum. The class of 1971 finished first overall on part one of the boards and finished first in all six categories. The class of 1972 finished third, as did we. The faculty could not figure out what had gone wrong in that one year. I asked Dr. Lisco for his thoughts. "Richard," he said, "the faculty are very concerned and trying so hard to make you the best. No matter how hard they try, they just can't seem to ruin the students!" Great man.

David Altshuler, MD '90, PhD '90

I was an MD-PhD student and did my thesis with Connie Cepko in the Department of Genetics. She met with me every week and brought a laser-like focus to designing good experiments and helping me achieve my goals. Her example was always in my mind when I later became a mentor to my own students and fellows.

Edward Ussery, MMS '08

There were several people who I consider my mentors. The neurologist Galen Henderson was always willing to discuss matters with me. Laurie Raymond, MD '77, a psychiatrist, and Karen Wulfsberg, an education specialist at HMS, provided plenty of advice on how to deal with the culture on the wards and how to develop effective techniques for assimilating the material we needed to learn. Radiologist Michael Lev worked with me on a publication, and Robert Lees, MD '59, played multiple supportive roles during my time as an HMS student. David Cardozo, PhD '93, offered a sympathetic ear whenever I happened by.

Albert Menno, MD '56

Francis Moore, MD '39, a surgeon, was my first inspiration to continue with surgery.

Richard Reiling, MD '67

I really didn't have a single mentor throughout my years at HMS, but instead had multiple mentors who I respected and who gave me advice and direction. Because I wanted to be a neurosurgeon, Thomas Ballantine, MD '67, was my most notable mentor. But many great teachers and classmates were helpful during those wonderful, difficult years. I remember with great admiration the urologist Wyland Leadbetter who, on a nice Saturday afternoon in May, waited to have me as his sole assistant in surgery.

Michael Cardi, MD '77

The renal medicine expert Jeffrey Stoff was my first team attending, in 1977, during the first month of my internship in internal medicine at the former Beth Israel Hospital. Although we presented to him a simple, straightforward case of hyponatremia, I was impressed by the clarity of his review of the normal physiology of water excretion and the pathophysiology of the various causes of hyponatremia. This and other qualities about Jeff inspired me to become a nephrologist.



Alvin Poussaint



Harold Amos

Mary Flowers, MD '78

Harold Amos, AM '47, PhD '52, a noted microbiologist, and Alvin Poussaint, a psychiatrist and member of the HMS faculty, embraced me as an African American student when my face was still stinging from my experiences in segregated schools in the South. These strong professors inspired me to transcend race and gender. They convinced me that hard work, integrity, humility, and the conviction to serve humanity were equally as important as passing exams and making good grades. They taught me that I deserved to be at Harvard—that Harvard benefits from my African American experience. Grateful!



Kelly Orringer, MD '94

Doris Bennett, MD '49, was one of my Patient-Doctor preceptors. She was so gracious and kind, a wonderful role model for a budding pediatrician. As one of the pioneering women to become a medical student at HMS, she really inspired me.

"As one of the pioneering women to become a medical student at HMS, she really inspired me."

Herbert Adams, MD '65

Francis Moore, MD '39, was my mentor. Although a middling technical surgeon, Franny was a superb teacher. Whether instructing the lowly medical student or talking with the chief resident, he demanded that you know the patient better than you know your mom. He was always stimulating us to think creatively. "If you do not keep a list of possible diagnoses inclusively wide," he would say, "you will never make the diagnosis." With Franny, one always had to defend one's course of therapy, which we all did with one another later.

William Thorpe, MD '73

Grant Rodkey, MD '43, was my mentor. Although he is now 97 years old, he remains active in the surgery unit at the VA Medical Center in West Roxbury, Massachusetts.

Grant befriended me during my first year, contacted me frequently, advised me on important medical issues, followed my work at Mass General, and has remained my friend through the years. I communicate with him often.

Claire Broome, MD '75

As a student member of the first Joint Committee on the Status of Women, I received a lasting lesson from Dean Robert Ebert, who sent me and Eileen Shapiro, staff associate, to lobby in Washington for our idea of part-time residency training. We met with relevant committee staff and eventually the provision was included in the Health Manpower Act. The experience gave me a lifelong awareness of what could be accomplished with an idea, assertiveness, strategic persistence—and, possibly, the Harvard name.

Sarah Wood, MD '95

My mentor was adolescent medicine expert Robert Masland, Jr. He inspired me to pursue a career in pediatrics and medical education. Working with him at HMS and at Boston Children's taught me the importance of close-knit student-faculty relationships and the value and influence of critical role models. Since I left HMS, I have helped build an innovative new medical school, the Schmidt College of Medicine at Florida Atlantic University, and as the school's senior associate dean for medical education, I try to inspire medical students the same way he inspired me.

Thomas Ukena, PhD '74, MD '75

Hermann Lisco guided me through the MD-PhD program with kindness and wisdom.

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Nason Hamlin, MD '72

My mentor, Clifford Barger, MD '43, was a fine teacher, researcher, and human being. He led me to a great fourth-year research project at Mass General with John Powell. Our families kept in touch for many years after graduation.

Ernie-Paul Barrette, MD '90

Michael J. Barry, who now heads up the general medicine unit at Mass General, was my attending when I was a sub-I at that hospital. He served as a role model, showing me that one could be a general internist, a clinician-educator, and an excellent physician.

James Alonzo Nelson, MD '65

John F. Burke, MD '51, professor of surgery at Mass General, spent several evenings mentoring a small group of medical students. George Nardi, an expert on diseases of the pancreas, also helped me to encourage the use of fiberoptic endoscopes.

William Elkins, MD '58

Richard Warren, MD '34, influenced me to pursue surgery.

John Bullock, MD '68

David G. Cogan, MD '32, a professor of ophthalmology at HMS, helped me publish my first paper, which describes my invention of a device for looking in your own eye. It was in the *Archives of Ophthalmology*, titled "Auto-Ophthalmoscopy."

Kurt Isselbacher, MD '50

Fuller Albright, MD '24, was my mentor.



Francis Neelon, MD '62

My mentor was a ghost. In 1958, Francis Weld Peabody, MD 1907, was 30 years dead, but HMS students were still given his essay "The Care of the Patient." I read it and tossed it away. As an intern in 1962, something from Peabody's essay began to ring in my ears. I found and reread the essay and was astonished at how wise Peabody had become in four short years. Dozens and dozens of rereadings always give me something new and timeless. I thank Harvard for putting his work in my unreceptive and unworthy hands.

Thank you to all who shared a memory of the people who mentored you while you were at HMS, and, in many cases, after your student days.

The next issue of Harvard Medicine *will feature your responses to the question:* ***What would you say to someone who asks you if they should become a doctor?***

Responses can be submitted online at https://hms.harvard.edu/rounds. Responses can also be submitted via email: hmsalum@hms.harvard.edu; phone: 617-384-8520; or by mail: Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Boston, MA 02115.



Richard Krueger, MD '73

Hermann Lisco, Raquel Cohen, MD '49, and Daniel Funkenstein mentored me while I was at HMS. All were terrific. Lisco, who taught anatomy, was in charge of prodigal medical students, so he saw me during the many years in which I took a leave of absence, withdrew, then reapplied to HMS. He was extraordinary. Cohen was my advisor in community psychiatry and was helpful, and Funkenstein followed my progress when I returned.

Obituaries

1930s

1939

Daniel S. Ellis, MD
December 13, 2017

1940s

1945

Jack S. Parker, MD
February 9, 2018

1946

John W. Braasch, MD
September 9, 2017

Richard W. Scott, MD
October 21, 2017

Alan D. Watson, MD
November 22, 2017

John A. Wood, MD
September 17, 2017

1947

Frank G. Bucknam, MD
February 17, 2018

Walter S. Rothwell, MD
December 27, 2017

Marvin H. Sleisenger, MD
October 19, 2017

1948

James A. Bougas, MD
October 28, 2017

Eugene D. Brand, MD
February 7, 2018

Ronald M. Ferry, Jr., MD
November 11, 2017

1949

Douglas V. Crook, MD
September 24, 2017

Stanley J. Wolfe, MD
January 11, 2018

1950s

1950

Elmer E. Batts, MD
September 4, 2017

Marvin L. Sachs, MD
January 29, 2018

Cyril E. Shea, Jr., MD
November 10, 2017

1951

David M. Bikoff, MD
November 1, 2017

1952

Stanley W. Kent, MD
December 13, 2017

Robert T. Potter, MD
February 1, 2018

1953

Daniel D. Federman, MD
September 6, 2017

Flaviu C. Romanul, MD
October 8, 2017

Earle N. Rothbell, MD
December 20, 2017

1954

Diane T. Brukardt, MD
February 17, 2018

James M. Hitzrot II, MD
December 20, 2017

James F. Marks, MD
October 2, 2017

Arthur G. Ship, MD
September 24, 2017

1955

Ronald R. Fieve, MD
January 2, 2018

James C. Pierce, MD
February 2, 2018

Norton G. Waterman, MD
October 6, 2017

1956

Nathaniel D. Greenberg, MD
October 22, 2017

Joseph P. O'Malley, MD
December 12, 2017

1957

John B. Josimovich, MD
October 7, 2017

Arthur J. Moss, MD
February 14, 2018

Victor W. Sidel, MD
January 30, 2018

1958

Paul J. Cannon, MD
January 2, 2018

1959

Richard E. Conway, MD
November 18, 2017

1960s

1960

Robert L. Shirley, MD
November 27, 2017

1961

John D. McGavic, MD
January 5, 2018

1963

Agnes Mayer Huber, PhD
September 29, 2017

1964

William D. Strathmann, MD
February 11, 2018

1965

Michael C. Beachley, MD
January 13, 2018

1966

Jack C. Bunn, MD
February 13, 2018

1968

John H. Brandt, MD
September 24, 2017

George A. Ellsworth, MD
December 29, 2017

1970s

1970

Robert H. Breed II, MD
December 9, 2017

Frederic E. Hyman, MD
October 11, 2017

1978

Timothy J. Batchelder, MD
January 2018

Earnest Wu, MD
September 17, 2017

1980s

1985

Edward G. Murphy, MD
October 15, 2017

1987

Lorraine E. Stanfield, MD
September 13, 2017

1990s

1990

Ben Barres, PhD
December 27, 2017

This listing of deceased alumni includes those alumni whose notices of death were received between September 1, 2017, and March 30, 2018.















Coast to Coast

In late 2017, Dean George Q. Daley, MD '91, set out on a Meet the Dean tour to share with alumni and friends his vision for the future of HMS. At the first event, in Boston, we asked alumni in attendance, "Who was your dean?" Recollections varied, but the stories were rich and enjoyable for the insights they offered of the people who have occupied pivotal roles at HMS throughout the past several decades.

Harvard Medicine asked the same question of alumni attendees at the Meet the Dean events that followed in Los Angeles, New York City, Philadelphia, San Francisco, and Washington, DC. We were delighted by the responses and hope you are, too. You'll find them at magazine.hms.harvard.edu/conflict/coast-coast

PRESIDENT'S REPORT

Excitement and Inspiration



AS I WRITE, THE SPRING WEATHER AND LONGER DAYS are bringing renewed energy to the HMS campus. The preclinical students are starting to learn histories and physicals, the core clerkships are keeping everyone busy in the hospitals, and the senior students are immersed in electives, research projects, and international experiences.

The Alumni Council convened its winter 2018 meeting in early February. Our agenda included reports on alumni engagement efforts, the new Office of Educational Quality Improvement, news on reunion plans, and an update on the School's campaign. Council members were eager to come together and discuss ways to further support the initiatives of Dean George Q. Daley, MD '91.

The Council is making strides within three areas: diversity, idealism, and community. Our work has so far resulted in new events that will bring together students and alumni from groups underrepresented in medicine, provide a gathering for recent graduates and for those attending fifth through fifteenth reunions, and again bring together the Society of the Silver Stethoscope (post-sixtieth reunion) alumni.

The Council is partnering with Dean Daley as the School anticipates LCME reaccreditation next year. We are working to identify ways that alumni can provide perspective on the medical education curriculum.

Two remarkable MD-PhD students presented their research at our meeting. Anthony Nguyen, PhD '16 MD '18, described the role of the ubiquitin proteasome system during terminal red blood cell development, and Katie van Schaik, MD '18 PhD '18, discussed the development and evolution of disease classification methods and treatment algorithms in ancient Greek medicine. Each time I interact with an HMS student, I am inspired. The future of medicine and biomedical research in the hands of this next generation is bright.

This is an important time to be engaged with HMS. To quote Dean Daley's recent letter to the HMS community, "While the technology may have evolved, the noble calling to serve those suffering from illness and disability has not changed … it's only through service and working together that we can make progress."

I invite and encourage you to engage with HMS, with your class, and with the Council to help advance the School's mission to cure disease and alleviate human suffering—a mission that inspired many of us to apply to HMS in the first place.

Elizabeth (Lisa) Petri Henske, MD '85, is an HMS professor of medicine at Brigham and Women's Hospital, director of the Center for LAM Research and Clinical Care at Brigham and Women's, director of the Brigham Research Institute, associate member of the Broad Institute of MIT and Harvard, and a medical oncologist at the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute.

Alumni Announcements

Reunion

Alumni from HMS classes ending in 3 and 8 and their guests are invited to rediscover the campus and rekindle friendships during the 2018 reunion festivities, May 31 to June 2. Events include a gala, faculty and alumni symposia, class-specific events, a family picnic, and much more. **Visit hms.harvard.edu/reunion for details and to register.**

Alumni Day: June 1

All alumni are invited to attend the dean's State of the School Address, the Harvard Medical Alumni Association's annual business meeting, the Alumni Day symposium, campus tours, and more. Members of the Society of the Silver Stethoscope—alumni who have celebrated their sixtieth reunion—are also invited to a private lunch with student guests and the HMS dean. **Visit hms.harvard.edu/alumni-day for details and to register.**

Recent graduates gathering in Boston

Come enjoy the city's nightlife with fellow recent grads on June 1 at the Rooftop@Revere in the Revere Hotel Boston Common. All alumni who graduated after 2003 are welcome. **To register or get more information, alumni graduating in 2003 and after should visit hms.harvard.edu/recent-graduate-gathering.**

Cast your vote in the Alumni Council election

This year's nominating committee has assembled an outstanding slate of candidates to serve on the Alumni Council. **View candidate profiles and personal statements before you vote online at hms.harvard.edu/election.** Votes must be received by Monday, May 28, at noon ET.

Online continuing medical education courses: 25 percent off

Continue your education with self-paced online courses taught by the School's renowned faculty. The HMS Global Academy has both accredited and nonaccredited content available for medical professionals. **Visit globalacademy.hms.harvard.edu and enroll using the code Alumni25 for the discount.**



HARVARD MEDICAL SCHOOL

"My gift reassures me that I have some part in the future and excellence of Harvard Medical School."

— Martin Mihm Jr., MD
Director, Mihm Cutaneous Pathology Consultative Service
Director, Melanoma Program, Department of Dermatology
Brigham and Women's Hospital

A LASTING LEGACY

Martin Mihm has been a member of the Harvard Medical community since the 1960s when he was a dermatology resident at Massachusetts General Hospital. In addition to significant donations, he has included HMS in his estate plans to leave his mark on the institution that has been such an important part of his life.

JOIN HIM IN LEAVING A LEGACY AT HMS.

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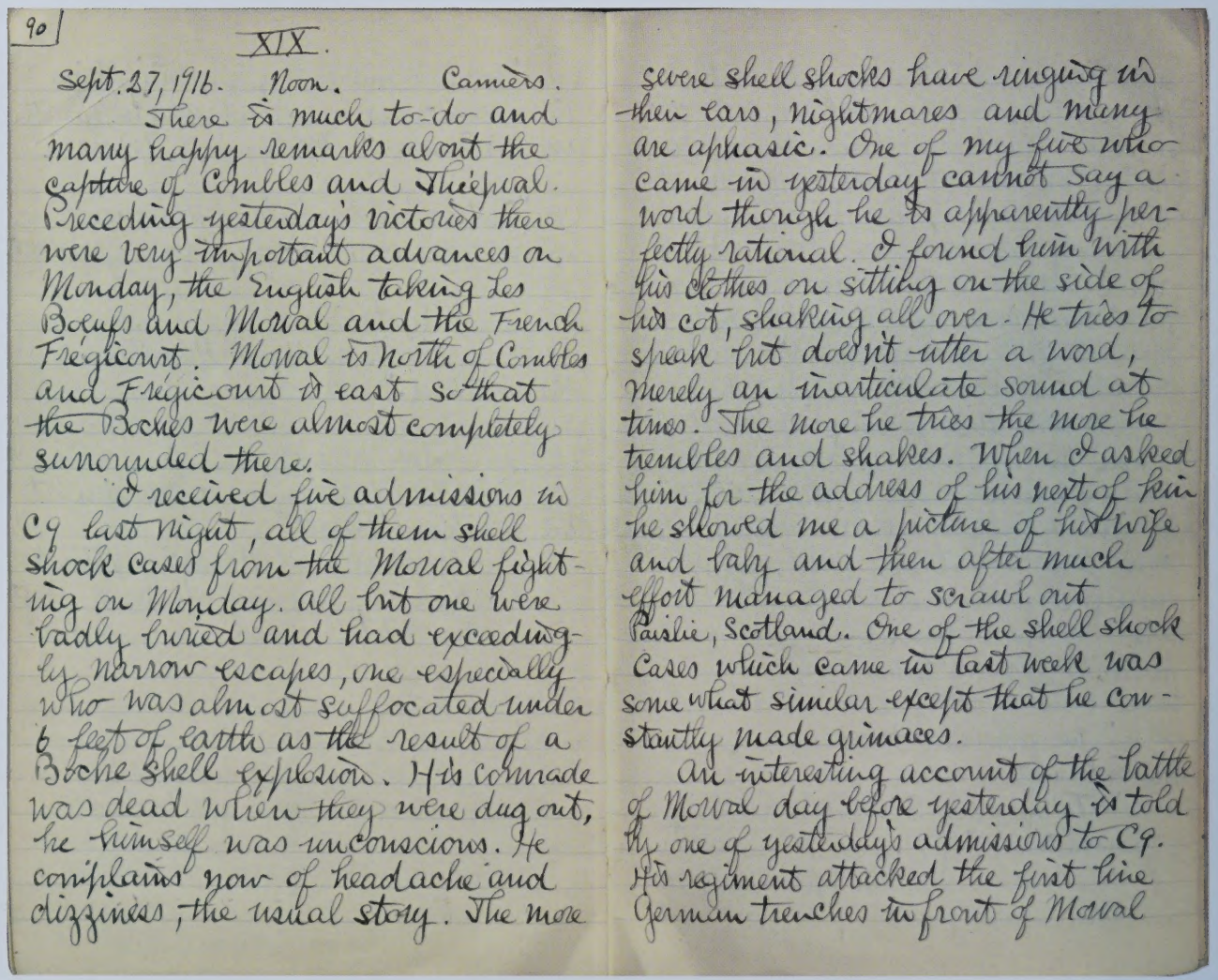
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In Camiers

In 1916, as a member of the Harvard Surgical Unit during World War I, Paul Dudley White, MD 1911, served at the British Army's No. 22 General Hospital, located in Camiers, France. He kept a diary throughout his days there and during the war years that followed. In the pages pictured here, he relates the stories of some young men who had been admitted to the hospital as "shell shock cases."

"All but one were badly buried...one especially who was almost suffocated under 6 feet of earth as the result of a Boche shell explosion. ..."

Records such as White's help scholars trace how the traumas of war have psychologically affected those who experienced them, an understanding that helps inform current work on post-traumatic stress disorder.



90

XIX.

Sept. 27, 1916. Noon. Camiers.

There is much to-do and many happy remarks about the capture of Combles and Thiepval. Preceding yesterday's victories there were very important advances on Monday, the English taking Les Boeufs and Morval and the French Frégicourt. Morval is north of Combles and Frégicourt is east so that the Boches were almost completely surrounded there.

I received five admissions in C9 last night, all of them shell shock cases from the Morval fighting on Monday. all but one were badly buried and had exceedingly narrow escapes, one especially who was almost suffocated under 6 feet of earth as the result of a Boche shell explosion. His comrade was dead when they were dug out, he himself was unconscious. He complains now of headache and dizziness, the usual story. The more severe shell shocks have ringing in their ears, nightmares and many are aphasic. One of my five who came in yesterday cannot say a word though he is apparently perfectly rational. I found him with his clothes on sitting on the side of his cot, shaking all over. He tries to speak but doesn't utter a word, merely an inarticulate sound at times. The more he tries the more he trembles and shakes. When I asked him for the address of his next of kin he showed me a picture of his wife and baby and then after much effort managed to scrawl out Paisley, Scotland. One of the shell shock cases which came in last week was somewhat similar except that he constantly made grimaces.

An interesting account of the battle of Morval day before yesterday is told by one of yesterday's admissions to C9. His regiment attacked the first line German trenches in front of Morval